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Symposium on

The Interrelationship between Pediatric Disorders and Nutrition

THE science of nutrition has perhaps contributed more to modern pediatrics than to any other branch of clinical medicine. The child is more susceptible than the adult to dietary privations. His reserves are more limited and his mechanisms for the digestion and assimilation of foodstuffs are more vulnerable. The striking reduction in infant mortality which occurred in well-developed countries from the middle of the last century onward was in large part achieved through a better understanding of nutrition.

Pediatric nutrition began with empirical observations on infant feeding in health and disease. An important advance was initiated in the last century by the German school of pediatricians, notably Czerny, who carried out pioneer studies of infant metabolism and observed the effects of unbalanced diets. They had a great influence on American thought and practice, but it was not until after the turn of the century that an American school developed under John Howland where biochemical technics were applied to clinical problems. The technics of blood chemistry came at this time and added greatly to knowledge obtained from balance studies; they were particularly fruitful in the field of electrolyte metabolism.

The study of nutrition in small experimental animals and the discovery of the vitamins and their corresponding deficiency diseases followed quickly upon this and produced a great change in pediatric thinking. The importance of ascertaining and meeting the requirements of the various nutrients was now recognized. The emphasis was no longer on tolerance and intolerance of foods for it became clear that the syndrome formerly attributed to toxic products from undigested food—"alimentary intoxication" was in reality a deficiency syndrome caused by dehydration. Parenteral nutrition made great strides in the succeeding years in the attempt to provide nutrients which a disordered intestinal tract would not readily assimilate.

It seems as if our knowledge of the fundamental nutritive requirements of the growing human being is nearing completion. Perhaps one or two additional accessory factors will be discovered, but the success with feeding synthetic diets for considerable periods of time makes it seem unlikely that there can be many such. Our goal of a completely adequate parenteral nutrition which will supply these nutrients adequately

by the parenteral route, as yet unrealized, seems not so far off.

The big problem of nutrition today is that of the nutritional requirements in disease. There are many indications of special nutritive requirements for particular diseases, and only a beginning has been made in studying them. Requirements in disease may differ not only quantitatively but qualitatively. In the last analysis cells die because some nutrient is not available. It may be some substance, important in intermediary metabolism, which the normal cell is able to manufacture which in the presence of disease cannot be manufactured. Thus a whole host of "conditional nutrients" required in particular disease states may in time be discovered. Some of these will perhaps be complex large molecules that cannot readily be supplied from without, but it may be possible to supply parts of the molecule—co-factors —that will serve the purpose. A particularly fruitful area for research in this field is the immature infant who lacks a number of enzyme systems possessed by his more mature brother. It is not unlikely that there exist for him a variety of special vitamins not needed in the older subject.

In selecting contributors to this symposium we have attempted to include topics in which nutritional therapy is a matter of practical importance. We have also endeavored to illustrate different categories of nutritional problems. The paper by Scrimshaw and associates on protein malnutrition defines a condition which is at present in the forefront of interest as a public health problem in technically underdeveloped countries but which is by no means confined to them. The paper by Pratt deals with the current status of water and electrolyte requirements. Those who feel that human milk has lost all its mystery may have their complacency a little disturbed by the observations of Mellander and Vahlquist which point to particular chemical factors of nutritional value in that fluid. The paper by Lahey highlights an area in which practice has not kept pace with nutritional knowledge. Iron deficiency, it seems, is still with us and newer types of nutritional anemia are making their appearance. Vitamin therapy has done us an invaluable service in eliminating rickets and scurvy, but evidence of overzealous prophylaxis should give us pause, as exemplified by "idiopathic hypercalcemia," described by Stapleton.

Three papers in the symposium deal with special nutritive requirements in pathologic states—that by Hunt illustrating a condition in which an excess of pyridoxine is needed, whereas the papers on galactosemia and phenylketonuria deal with conditions in which a reduced quantity of a normal nutrient is the key to therapy. The subject of inborn errors of metabolism is attracting ever-increasing interest since it has been shown that some of them at least are susceptible to correction by diet. In this connection reference should be made to the recent symposium on this subject* and to the cogent introductory remarks of its editor, Professor Dent.

Although the limitations of space have prevented the inclusion of many areas of pediatric nutrition we hope that this brief collection will prove as interesting to our readers as it has to the editors.

PAUL GYÖRGY
L. EMMETT HOLT, JR

* Am. J. Med. 22: 671, 1957.

On the Evaluation of Artificial Feeding

By OLOF MELLANDER, M.D.,* AND BO VAHLQUIST, M.D.†

THE NUTRITIONAL value of different diets can be analyzed in two ways: (1) by detailed study of the chemical composition of the nutrient in question and (2) by study of the effect of the nutrient upon the consumer. In the case of infants, these studies are relatively simple, for the main constituent of their diet, milk, is a homogenous foodstuff.

Hitherto the effect of various infant diets has been studied mainly by recording their effects on the infant's weight, frequency of stools and the like. But, as more has been learned about the complicated chemical structure of milk, it has become apparent that this method does not give enough information. In this paper we shall give a brief survey of some aspects of the chemical structure of milk proteins and also describe plans for a study to determine how human and cow's milk affect other conditions such as blood chemistry, antibody formation, and osseous development.

CHEMICAL ASPECTS

Milk proteins are considered to be of high nutritional value. Animal experiments have shown that they are better than other proteins in causing an optimum gain in weight during the growth period. This is true of the total proteins from both human and cow's milk. Only egg proteins are more effective in this respect, and they too are meant for nutrition at an early stage of life.

In every kind of milk the protein consists of a complex system, including casein and its subfractions, the albumins and globulins of the whey fraction, and a number of other proteins, some of a poorly defined nature. Casein is the most interesting of these, as it is a type of phosphoprotein found only in milk. The protein stores in the egg also contain a large amount of phosphoproteins. These substances, consequently, are a common component of the most valuable nutritional proteins.

The proportion between casein and total whey protein is very different in human and cow's milk. Human milk contains only about 0.5 per cent casein, whereas cow's milk contains about 3 per cent. Even when cow's milk is diluted with an equal volume of water—still a common way to prepare milk for infants—it contains about three times as much casein as human milk. In more concentrated mixtures the difference is still greater. In some of the modern cow's milk preparations this difference is eliminated.

If the only way protein contributed to nutrition was by supplying the essential amino acids, this difference would play no part, for milk proteins all contain about the same amount of amino acids, and no matter what sort of milk protein was used, adequate amounts of essential amino acids would be supplied. However, there are many facts which indicate that proteins not only serve to convey the essential and other amino acids, but also have more specific tasks connected with specific features of their chemical structure. Thus it is known that the immune globulins in cow's colostrum protect the newborn calf against various infectious diseases and that the casein plays a part in the absorption of calcium and phosphorus. Differences in chemical structure and in biologic properties are therefore of great interest, especially when comparing corresponding proteins in human and cow's milk.

If, to begin with, one studies the enzymatic digestion of the total proteins in the milk, one makes the puzzling observation that the proteins in cow's milk are broken down much

* Professor of Medical Biochemistry, University of Gothenburg.

† Professor of Pediatrics, University of Upsala.

From the Department of Medical Biochemistry, University of Gothenburg and the Department of Pediatrics, University of Upsala.

faster than the proteins in human milk. Figure 1 shows the rate of hydrolysis in the infant's stomach.[1] As is seen there, very little of the human milk protein is split up. This difference in digestion of the proteins of cow's and human milk is partly due to the fact that the casein of human milk is much more difficult to hydrolyze than the casein of cow's milk.[2] This, in turn, is because a part of the casein molecule is resistant to the proteolytic enzymes in the alimentary tract. This part of the molecule is found as a peptide mixture after the casein is digested with pepsin and trypsin and has the amino acid composition shown in Table I. The reason for the resistance to enzymatic

TABLE I

Amino Acid Composition of Phosphopeptides from Cow's Casein

	%
Aspartic acid	4.5
Threonine	2.5
Serine	12.2
Glutamic acid	18.5
Proline	1.4
Glycine	1.1
Alanine	1.1
Valine	2.9
Isoleucine	6.0
Leucine	1.6

hydrolysis is that serine is esterified with phosphoric acid. The phosphorus content is about 7 per cent. This resistance to proteolytic enzymes of the phosphorylated peptides sets up the conditions for direct absorption of these compounds.

As mentioned, much more of the phosphorus in human milk casein is recovered in peptide form than in cow's milk casein.[2] However, there is about twice as much phosphorus in cow's milk casein. It is not yet clear whether there are any significant nutritional differences between the peptide residues of human and cow's casein.

Since the phosphoric acid residues of the serine peptides permit a complex formation of metals, what is absorbed probably consists of compounds with the metals present in the alimentary tract. The physicochemical basis for

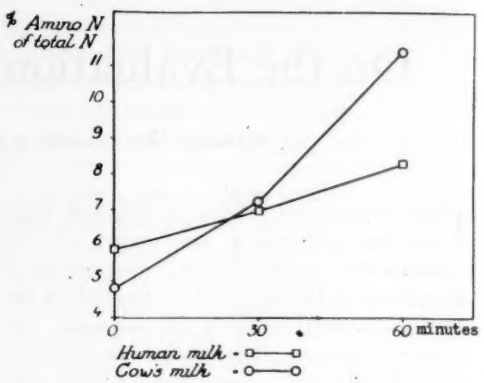

Fig. 1. *In vivo* digestion of cow's and human milk (in the infant's stomach). From: Berfenstam, R., Jagenburg, R., and Mellander, O.: *Acta Paediatrics* 44: 348, 1955.

this complex formation has been studied by Österberg.[3] The calcium salt of the peptides contains not less than 10 per cent calcium in soluble form and it is quite possible that it is used as a source of mineral for ossification of the bones.[4,5] Calcium is not the only mineral which is bound. There is more calcium than there are other minerals in milk, therefore, the calcium salts predominate, especially in cow's milk. Because of this, there is a risk that the other metals, for example, iron, are displaced from the peptide carrier. This may favor the development of anemia in artificially fed infants. Even other minerals which occur in small quantities, e.g, cobalt, may be displaced from the peptides. There is much less risk of this when human milk is given, because of its lower content of all minerals, especially calcium.

This absorption of phosphopeptides may also be of interest from another point of view. It is known that protein metabolism proceeds to a large extent via phosphorylated amino acids and peptides. It seems reasonable to assume that these processes are facilitated if certain amino acids or peptides are given in phosphorylated form.

In this connection it should be mentioned that Johansson and Svennerholm[6] demonstrated large differences between the protein-bound carbohydrates in human and in cow's

TABLE II

Carbohydrate Content of Human and Cow Caseins (Values Given in Per Cent of Dry Weight)[6]

Casein	Hexosamine	Hexose	Sialic acid ($C_{11}H_{21}NO_{10}.H_2O$)	Total carbohydrates
Human	1.32	1.98	0.76	4.03
Cow	0.18	0.24	0.39	0.80

casein (Table II). These components are of interest, especially in relation to the microbial flora in the intestine, and should be considered in the light of recent observations of György and his co-workers.[7–9]

NUTRITIONAL ASPECTS

If the total amount of some of the most important nutrients given the infant during the first six months is calculated, it is seen that there are distinct differences between breast and bottle feeding. This is shown in Table III where the data for cow's milk are based on

TABLE III

Comparison between Total Amount of Various Nutrients Supplied by Human and Cow's Milk

	Breast feeding (135 liters of breast milk during 6 months) g	Cow's-milk feeding (160 liters of half-milk mixtures during 6 months) g
Calcium	45.9	89.6
Phosphorus		
Total-P	18.9	73.6
Casein-P	2.2	19.2
Total protein	1,620	2,720
Casein	540	2,400
Whey protein	1,080	320

the use of half-strength milk with 5 per cent sugar added. Thus 540 g of casein, for example, is obtained in the human milk, as opposed to 2,400 g in the cow's milk formula. The difference would have been still greater if a more concentrated formula had been used. Added to this are the aforedescribed differences in the quality of the two forms of milk. Since these differences both in quantity and quality are particularly large in the protein component, it is obvious that in biologic research one must pay particular attention to the functions that are directly connected with the supply of protein. This was done in planning the field study now to be described.

FIELD STUDY

In this connection, only a brief presentation of the organization of the study will be given as well as some data pertinent to the development of the skeleton. Some preliminary results were presented at the International Pediatric Congress in Copenhagen in July 1956.

It was found that Northern Sweden offered the best conditions for the investigation. The town of Kiruna and the rural districts of Töre and Råneå near the town of Boden were chosen. From June 1953 to December 1954, 402 newborn children were registered in these places. Before they were born, information was obtained about the family situation, about the physical condition of the mother and other members of the family, their food habits, living quarters, and the like. After the infant was born, it was carefully supervised by specially appointed nurses and every one or two months the infant had a medical check-up at the local welfare clinic. Thorough medical supervision was maintained until the child was one year old. After that the examinations were less frequent. Careful notes of all data relevant to the health situation were made in special records.

Feeding: The mothers were allowed to choose between breast and bottle feeding. In 26 per cent of the cases, the infants were nursed at the breast exclusively for at least six months. If weaning began earlier the mother's milk was supplemented by a formula of one part cow's milk and one part water, 5 per cent sugar and 1 per cent wheat flour. This formula gave about 550 calories per liter, and contained about 1.7 per cent protein, 1.5 per cent fat, 8 per cent carbohydrate, and 0.4 per cent minerals. The infant was allowed to get 600 to 700 g a day when it was one month old and afterward the amount was gradually increased until it reached 800 to 1,000 by the time the infant was three months old. When it was four months old, crushed rusks were added to one or two of the feedings. In one part of the series the food was prepared from fresh cow's milk and in the other

from a dry milk preparation giving the same composition of the mixture used.

The diet was also supplemented as follows: From the age of one week onward 10 drops of a vitamin-preparation were given, which provided 2,500 units of vitamin A and 1,000 units of vitamin D a day. This dose was doubled at three months. At three months 25 mg of ascorbic acid were given a day, together with fruit juice or an infusion of rose-hips (a source of ascorbic acid). Strained baby foods were introduced at four months. During the period of the investigation no pressure was exerted on the mothers to breast feed the infants. On completion of weaning, at seven to eight months, all groups were receiving the same amount of milk, corre-

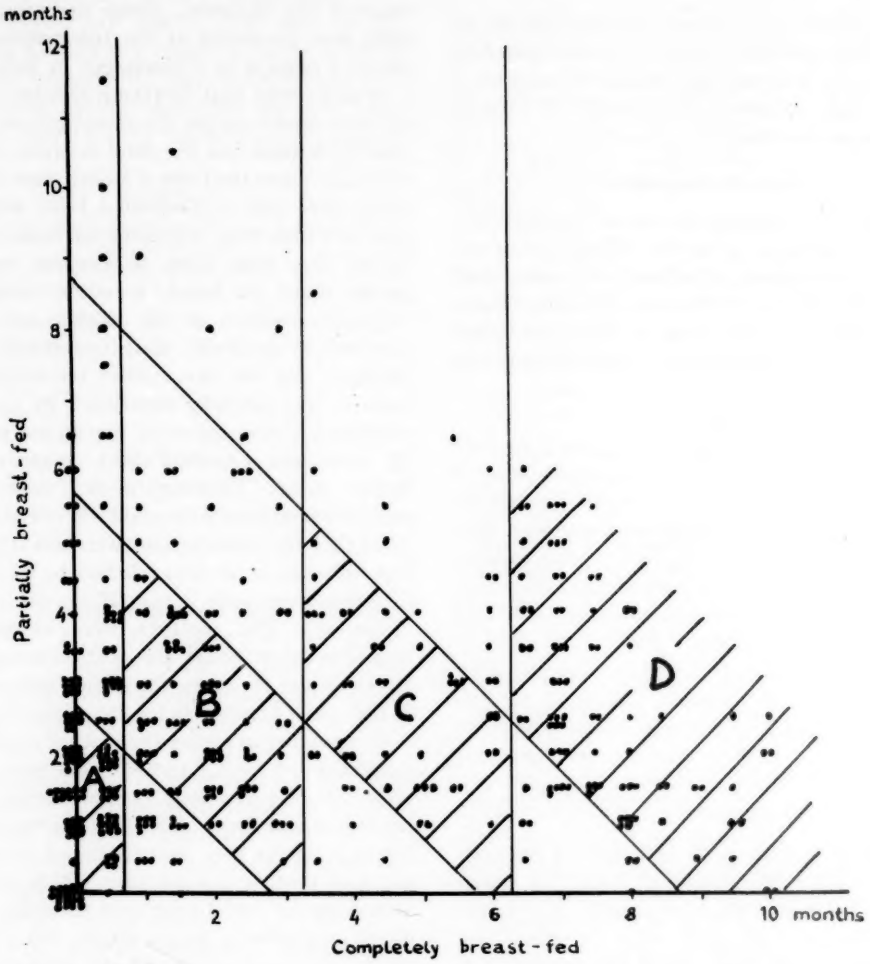

Fig. 2. Presentation of the whole material with respect to the period of complete and partial breast- feeding for each single subject. Each dot represents one child. Classification into groups A, B, C, and D (hatched areas) comprising 274, out of a total of 402 children.

Group A (weaned early) includes 88 children.
Group B (intermediate group) includes 69 children.
Group C (intermediate group) includes 38 children.
Group D (weaned late) includes 79 children.

sponding to 0.6–0.7 liter of cow's milk per day.

Immunization schedule: BCG vaccination was done during the first week of life, and the tuberculin reaction tested at the age of three and seven to eight months. Combined vaccination (whooping cough, diphtheria, and tetanus) with 1 ml of vaccine was done at the age of three, four and one-half, and six months of age and smallpox vaccination generally between the ages of four and one-half and six months. In a limited group a vaccination against influenza virus was also included.

Special Examinations: In addition to the regular medical supervision of the children special examinations were done on the following three occasions: (1) at birth and at age seven or eight months, chemical and serologic analysis of blood, (2) at birth, roentgenographic study of the skeleton, and (3) at the age of two and one-quarter to three years (chemical and serologic analysis of blood and roentgenography of skeleton in half the cases and detailed examination of the teeth in the whole series).

Results: For further analysis, the series was divided into four groups, according to the duration of complete and partial breast feeding (Fig. 2).

The weight gain in the various feeding groups is given in Figure 3. The children with prolonged breast-feeding increased more rapidly in weight during the first three months but later on more slowly than the children weaned early. A complete report of the study will be presented elsewhere.

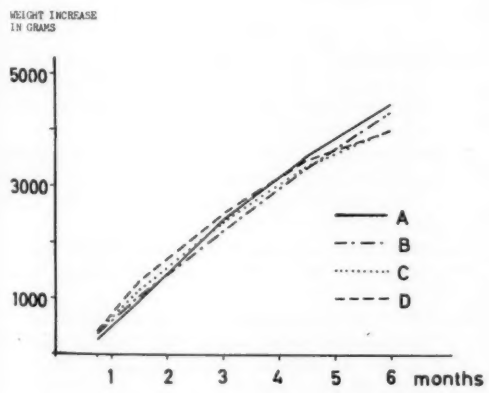

Fig. 3. Weight gain during the first six months of life. Classification into four different groups of feeding (*cf.* Fig. 2).

In view of the differences in the supply of proteins and minerals in breast feeding as compared with those in cow's milk feeding, we shall focus on a few observations concerning the development of the skeleton during the first year of life. This was judged partly by the growth in height and partly by the number of osseous centers seen in the roentgenogram. In addition, the amount of calcium, phosphorus, and alkaline phosphatase in the blood in the various feeding groups was determined. The condensed data are presented in Table IV. In the first place a comparison was made between two extreme feeding groups (A and D) but the findings in the other groups (B and C) are also referred to. It is evident from the results presented in Table IV that the children weaned early (group A) were significantly taller than those weaned late (group D).

The centers of ossification were evaluated according to Elgenmark.[10] This technic involves counting all the centers of ossification in the arm and leg of one side of the body. The results of this procedure in the series now reported indicate that the appearance of the centers of ossification was hastened in group A (those weaned early) compared with group D (those weaned late).

No definite case of rickets was encountered in this investigation, which shows that the health supervision and administration of supplementary vitamins was carried out faithfully.

Serum calcium, phosphorus, and alkaline phosphatase levels were determined at seven to eight months. The different feeding groups had similar calcium levels. The values for serum phosphorus and alkaline phosphatase, on the other hand, are significantly lower in group D as compared with the other groups (Table IV).

The differences observed in height, in the number of osseous centers and in certain blood chemical data are mostly small in absolute values but are nevertheless statistically significant. It would seem reasonable to assume that they are correlated with an increased rate of deposition of calcium and phosphorus in infants reared on cow's milk formulae.

TABLE IV

Average Height and Number of Centers of Ossification at Seven and One-half Months. Average Serum Calcium, Serum Phosphorus, and Serum Alkaline Phosphatase at Seven to Eight Months of Age. The Series is Divided into Four Groups, According to the Mode of Rearing (A, Extreme Cow's-Milk Group; D, Extreme Breast-Milk Group)

	Total number examined	Feeding groups (of Fig. 2)				
		A	B	C	D	Difference
						D − A
Height, cm	274	70.15	69.77	69.07	69.05	−1.10†
Number of osseous centers	274	14.0	13.25	13.05	13.05	−0.95†
						D − (A and B + C)
Serum calcium, mg/100 ml	112	10.25	10.35	10.30	10.45	0.15
Serum phosphorus, mg/100 ml	136	6.19	6.28	6.39	5.75	−0.51‡
Serum alkaline phosphatase, units/ml	131	18.54	18.43	19.02	16.31	−2.29†

† Significant at the 1%-level.

‡ Significant at the 1‰-level.

A more detailed presentation of the material is given in a paper by Vahlquist, Mellander, and Wickslund.[11]

The fact that infants weaned at an early stage grow and show skeleton maturation at a slightly increased rate does not imply that they are superior in other respects. In forthcoming papers it will be demonstrated that the formation of antibodies against diphtheria and whooping cough is much the same irrespective of the type of feeding, but that the combined incidence of upper respiratory infections, otitis, and diarrhea is significantly higher among the babies weaned early (group A) than among the babies weaned late (group D). It would seem, therefore that the nutritional value of a food can be assessed correctly only by detailed and careful clinical and biochemical studies. The field study discussed above is a step in this direction.

SUMMARY

The supply of various nutrients differs greatly, quantitatively as well as qualitatively in breast-milk feeding as compared with cow's milk feeding. Even if a cow's milk formula is modified to imitate breast milk in its gross chemical properties it is not necessarily superior to other more traditional formulae.

ACKNOWLEDGMENTS

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REFERENCES

1. Berfenstam, R., Jagenburg, R., and Mellander, O.: Protein hydrolysis in the stomachs of premature and full-term infants. *Acta Paediat.* 44: 348, 1955.
2. Mellander, O.: On chemical and nutritional differences between casein from human and from cow's milk. *Upsala Läkaref. Förh. Ny Följd* 52: 107, 1947.
3. Österberg, R.: Metal and hydrogen-ion binding properties of O-phosphoserine. *Nature* 179: 476, 1957.
4. Mellander, O.: Importance of the casein phosphopeptide calcium salts. II. Peroral calcium dosage in infants. *Upsala Läkaref. Förf. Ny Följd* 55: 247, 1950.
5. Mellander, O., and Isaksson, B.: The physiological importance of the caseinphospho peptide calcium salts, I. Intravenous and

peroral calcium dosage in animal experiments. *Upsala Läkaref. Förh. Ny Följd* 55: 239, 1950.

6. JOHANSSON, B., and SVENNERHOLM, L.: The content of carbohydrates in caseins from different species. *Acta Physiol. Scand.* 37: 324, 1956.
7. GYÖRGY, P.: Hitherto unrecognized biochemical difference between human milk and cow's milk. *Pediatrics* 11: 98, 1953.
8. GYÖRGY, P., NORRIS, R. F., and ROSE, C. S.: Bifidus factor, variant of lactobacillus bifidus requiring special growth factor. *Arch. Biochem.* 48: 193, 1954.
9. ZILLIKEN, F., BRAUN, G. A., and GYÖRGY, P.: "Gynaminic Acid" and other naturally occurring forms of *N*-acetylneuraminic acid. *Arch. Biochem.* 63: 394, 1956.
10. ELGENMARK, O.: The normal development of the ossific centres during infancy and childhood. *Acta Paediat.* 33: (Suppl. 1), 1946.
11. VAHLQUIST, B., MELLANDER, O., and WICKSLUND, H.: Breast milk and cow's milk in infant feeding. Skeletal development during the first year of life. *Ann. Paediat. Fenn.* (to be published).

Failure to Gain Weight

By L. EMMETT HOLT, JR., M.D.*

THE INFANT or young child who fails to gain weight properly without any obvious disturbance of digestion presents an interesting and a puzzling clinical problem. Where does the food go? We put in a normal quantity of a normal food. The excreta do not seem to be in any way abnormal and yet gain in weight is either stationary or minimal. Sometimes this situation is encountered after an acute illness, sometimes it follows some chronic disorder; in still other cases it cannot be related to any antecedent or precipitating disease and is evident in very early infancy. In New York City we encounter this problem not very infrequently among immigrants from Puerto Rico, whose diet and living conditions have been substandard, but it is by no means confined to this group. We correct the diet, and rid these children of such parasites as they may have. Yet often for many months they do not gain weight and grow properly. Where does the energy go?

The few experiments of Siwe[1] in which bomb calorimetry of excreta were carried out failed to reveal unusually large losses by these routes. Observations by Levine and others[2] showed a somewhat greater basal heat production in these infants per unit of body weight, but not enough to account for their failure to thrive. It is difficult to reconcile these observations with the first law of thermodynamics.

There are, however, several possible explanations of this apparent paradox, and it is the purpose of this communication to call attention to several that we have encountered. An appreciation of their nature may help, in some instances at least, to better therapy.

From the Department of Pediatrics, New York University College of Medicine and the Children's Medical Service, Bellevue Hospital, New York, N. Y.

* Professor of Pediatrics, New York University College of Medicine, Director Pediatric Service, Bellevue Hospital, New York, N. Y.

In many instances, failure to gain weight is caused by unappreciated losses of nutrients in the excreta. One of the first of these conditions to come to my attention was that of *masked steatorrhea*. An excess of fat may be lost in the stools, although the gross and often the microscopic appearance remains quite normal. I became aware of this condition some years ago in Baltimore when we were running fat balance studies on normal babies fed different kinds of fat.[3] From time to time one of our subjects would pick up an infection and develop diarrhea, necessitating an interruption of the study. We would wait for this to subside, allowing a few days in addition for good measure before resuming the study, but almost invariably the findings of the first period after the infection had to be discarded because of an unsuspected steatorrhea. The water and electrolyte losses had ceased and the stools were no longer loose, but fat absorption had not yet returned to normal. The time required for the assimilation of fat to return to normal varies greatly in individual infants. It may be very prompt, requiring only a few days or it may last for a longer time. If it is sufficiently delayed and the fact is recognized, we label the child a celiac. One of the most striking examples of latent steatorrhea is the steatorrhea of the premature infant. The stools in these infants appear normal even though as much as 50 per cent of the ingested fat is being lost. Here, too, a microscopic study of the stool reveals no abnormality.

A simple remedy for steatorrhea is to make up for the loss of calories by an increased caloric intake. This can be done perfectly well by adding carbohydrate or protein. We have shown, however, that it can also be done in all the forms of steatorrhea that we have studied[4–7] by giving additional fat. When more fat is added the proportion of absorbed fat remains unchanged. More is excreted in

the stool, to be sure, but more is absorbed, and we have found no evidence that unabsorbed fat is in any way harmful or causes losses of other nutrients as has been feared by some.

Are there conditions in which there is masked loss in the stools of nutrients other than fat? Loss of nitrogen is rarely obvious to the eye. But it is well recognized that when the digestive secretions are impaired considerable unsplit protein may escape digestion. The most familiar example of this condition is cystic fibrosis of the pancreas in which we attempt to overcome this defect by giving more protein. Lesions of the pancreas differing somewhat from cystic fibrosis have been observed in states of severe chronic protein deficiency known as malignant malnutrition, *kwashiorkor*, and by various other names. That serious fecal loss of nitrogen may occur in this condition is well known. This, too, has often been attributed to insufficiency of the digestive enzymes, but other factors also play a part. There is a depletion not merely of the digestive enzymes, but of body enzymes in general. The processes of assimilation of food as well as of digestion are affected and tissue synthesis throughout the body is impaired. Of the limited amount of nitrogen absorbed a substantial fraction cannot be used and spills out in the urine. Excessive nitrogen may thus be lost both in the urine and the stools.

We encounter occasional examples of kwashiorkor among Puerto Rican children who come to New York. We have also been fortunate in being able to collaborate with Dr. Federico Gomeź and his group in Mexico City in a study of that condition. The accompanying Table (Table I) shows one such patient in whom nitrogen balance studies were carried out at intervals. There is considerable variation in individual cases in the extent of the fecal and the urinary losses, but in this patient there were substantial losses by both routes. When first studied, immediately on admission, only 32 per cent of the nitrogen intake was being absorbed, the normal proportion being 80 to 90 per cent. One week later the figure had risen to 60 per cent, but it required two and one-half months before normal absorption figures were obtained. The urinary nitrogen loss of 0.82 g a day, a substantial loss for an intake of only 1.42 g, was decreasing on an identical intake a week later. The final high figure for urinary nitrogen is not relevant, since it reflects an exceptionally high nitrogen intake given just before the third period of study.

Further light upon the anabolic defect in these patients is shown in Table II which illustrates the result of a tryptophan load test carried out on admission and during the early and later recovery phase. Ingested L-tryptophan may be used for tissue synthesis or it may be degraded in various ways, one of the latter being the degradation through kynurenine to N-methyl nicotinamide (NMN), a compound

TABLE I

Nitrogen Balance in Kwashiorkor
Patient R.—12 months old

Period	I	II	III
Date	4/20–4/24	4/27–5/1	7/13–7/17
Diet	Tortilla and beans	Tortilla and beans Whole milk	Whole milk
Weight, av	5.0 kg	5.1 kg	6.2 kg
N intake, g/day	1.832	1.914	3.330
Stool N, g/day	1.240	0.760	0.487
Urine N, g/day	0.837	0.704	2.83
N absorbed, g/day	0.592	1.159	2.843
% intake absorbed	32.3	60.4	85.4
N retained, g/day	−0.244	0.456	−0.033

TABLE II

Tryptophan Load Test in Kwashiorkor
(Excretion of N methyl nicotinamide (mg)
After Ingestion of 1 g L-tryptophan)
Patient R.

Period	I	II	III
Day 1	0.81	0.55	1.97
Day 2	1.76	0.78	3.06
Day 3	5.18	0.75	1.98
Day 4	5.90	0.81	1.53

readily measured in the urine by its fluorescence. When first observed on admission this patient showed a marked and clear-cut excretion of NMN after the tryptophan load, the increased excretion lasting for several days. It was obvious from this that the kynurenine metabolic pathway was in good working order. From the second test, carried out a week later, one might be tempted to conclude that this pathway had failed since the test was completely negative, no increase in NMN being found. A more reasonable interpretation, however, in the light of the nitrogen balance study shown above, is that with the resumption of tissue anabolic processes, as indicated by the improved nitrogen retention, no surplus of tryptophan remained for degradation of NMN. Such degradation took place in the initial period only because the anabolic processes were not functioning properly. In the final period, two and one-half months later, when the anabolic needs had been to a considerable extent taken care of there is evidence of a return of the NMN excretion after the tryptophan load.

The management of the protein-starvation syndrome as usually stated is to give protein and to give it generously. This appears to make sense, but requires a certain amount of qualification. When food of any kind is withheld the adaptive enzymes responsible for metabolizing it suffer and the tolerance for that particular food is to some extent lost. This phenomenon has been known for a long time. In the case of carbohydrate it is known as Hofmeister's diabetes or "starvation diabetes." The individual who has been deprived of carbohydrate reacts for a few days like a diabetic when carbohydrate is freely supplied to him. In the case of fat a similar transitory loss of tolerance from disuse was described by Ivar Bang of Sweden,[8] a phenomenon which we ourselves observed in Baltimore. The situation in the case of protein deprivation is similar, but more serious than in the case of fat and carbohydrate in that adaptation appears to be less rapid, if one may judge from animal studies. The animal presented with an additional load of protein requires more liver tissue to deaminate it and more renal tissue to secrete the additional urea load. Hypertrophy of these two organs follows an elevation of the protein intake with great regularity.[9,10] When the protein load is introduced by the oral route the consequences are not too serious because of the impaired nitrogen absorption which I have illustrated above, which limits the uptake, but when hydrolyzed protein or amino acids are introduced intravenously fatal consequences may follow, as was discovered in the case of concentration-camp victims. Even with oral feeding of patients with kwashiorkor Dean and Schwartz[11] have reported that the nonprotein nitrogen of the blood rises to pathologic levels for some days which suggests a measure of caution in introducing protein food and the desirability of using both carbohydrate and fat at this time, since adaptation to these two foodstuffs is more quickly achieved.

Impairment of nitrogen retention results from failure of anabolic enzyme systems. The cause of such failure may be congenital or acquired. The conditions responsible for such failure differ in different parts of the world and are changing with us here. In underdeveloped countries inadequate food and infection, both products of ignorance and a low standard of living, are responsible for this. With us these obvious extrinsic causes are disappearing and we are learning to search for some intrinsic cause, some *silent metabolic anomaly* of which an ever-increasing number are coming to light. Some of these are transitory, of longer or shorter duration, and others are permanent. Metabolic anomalies interfere with gain in weight in two ways: (1) by causing impaired appetite, and (2) by causing masked caloric losses in the excreta.

The list of metabolic anomalies is a long one and is increasing every year. These entities are all rare, but the chance of encountering one of them is not so rare. Some metabolic anomalies although interfering with growth produce other more conspicuous symptoms which attract attention. Diabetes mellitus and nephrosis often involve serious caloric losses in the urine. Frequently recurring infections, such as may occur in agammaglobulinemia may cause serious losses in the stools as well as in the urine. We also have to consider a large and increasingly recognized group of "silent"

metabolic anomalies where the symptoms are insidious, perhaps confined to anorexia with a little vomiting and chiefly characterized by failure to thrive. Several of these syndromes are discussed in the present symposium: *idiopathic hypochloremic renal acidosis, idiopathic hypercalcemia and galactosemia.* The various forms of renal glycosuria, including the Debré-deToni—Fanconi syndrome should be mentioned among the conditions in which unusual caloric losses in the excreta take place.

A number of metabolic anomalies, some congenital and some acquired, are associated with aminoaciduria. They include vitamin D-deficient rickets, vitamin D-resistant rickets, the Fanconi syndrome, the Hartnup syndrome, galactosemia, phenylketonuria, cystinosis, cystinuria, Wilson's disease, and various other forms of liver disease, the aminoaciduria of the neonatal period and that caused by various poisons, notably lead. The loss of amino acids in some of these conditions may be as much as ten times the normal figure. However the absolute quantity of amino acids so lost remains small and does not *per se* cause a serious caloric deficit. Only in those conditions where there is an accompanying loss of sugar or some other caloric nutriment is there likely to be a caloric deficit. The metabolic anomaly exerts its effect largely by impairment of appetite.

There is, however, a different group of conditions associated with unexplained failure to gain weight, a group even more common than those referred to above. The following is a typical example:

Case Report: N.C. (#17594-55) was admitted to Bellevue Hospital at the age of 19 months because of failure to gain any appreciable amount of weight for the past year. His family history and the history of the pregnancy were in no way remarkable. His birth weight was 6 lb, 15 oz. He was breast fed for a few weeks only, being then put on an evaporated milk formula, solids and vitamins being added during the fourth month. He failed to thrive almost from the start and during his first eight months of life he added only 3 lb to his birth weight. From then on his weight remained stationary. At the age of eight months he had been admitted to another hospital for study because of his failure to gain weight, where he remained for the succeeding 11 months (Fig. 1). He was the subject of considerable interest on the part of the hospital staff and was studied in considerable detail.

Physical examination failed to reveal any definite cause for his malnutrition and failure to thrive. His appetite was not good, but with persistence a reason-

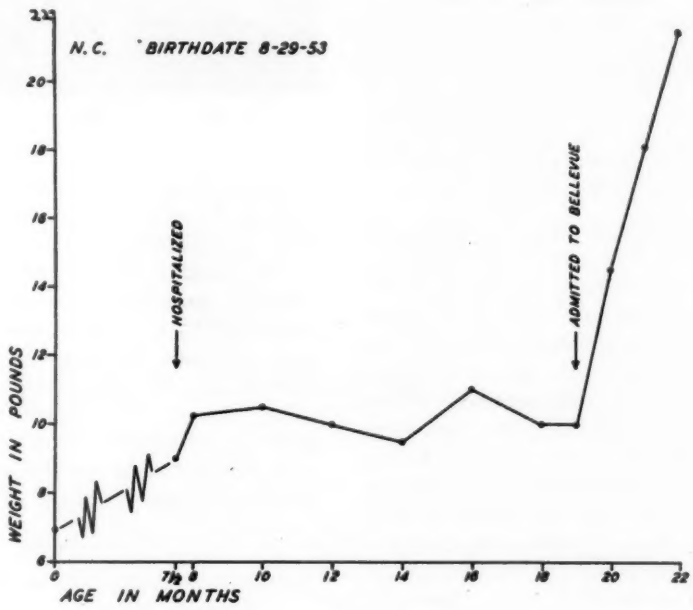

Fig. 1.

able amount of mixed diet was consumed. The bowels were quite normal. From time to time regurgitation of food was noted and some epigastric peristaltic waves travelling from left to right were seen. Barium swallow on one occasion revealed slight dilatation of the esophagus and reflux of barium from the stomach. A laparotomy was performed at the age of 17 months because of the suspicion that some malformation of the gastrointestinal tract was present but no such condition was discovered. An intercurrent respiratory infection, possibly related to aspiration was associated with fever for a time, but this did not persist.

Many laboratory studies were undertaken which failed to reveal anything abnormal. Therapy consisted in altering the diet to tempt the child's appetite, gavage when an insufficient quantity of food was taken; a variety of drugs were also tried including antispasmodics, thyroid extract, Thorazine®, and cortisone. None of these measures resulted in any gain in weight.

At the age of 19 months the possibility of some unusual metabolic anomaly was considered and the child was transferred to Bellevue Hospital for study. He then weighed 10 lb and presented a pathetic picture of extreme emaciation and apathy. Again physical examination and laboratory studies revealed no evidence of disease that would account for the picture. The food was reasonably well taken, but some regurgitation was noted. On close observation by the nursing staff it was found that the child was a persistent ruminator. This condition was treated by a concerted effort on the part of the nurses and house staff to divert the child after meals and whenever he started to ruminate. He was picked up, carried around, and given a great deal of personal attention. The therapy was successful and within a few days rumination ceased. Gain in weight began some 10 days after admission and continued without interruption. In the course of the next three months his weight doubled. He was discharged at the age of 22 months weighing 21½ lb (Fig. 2).

It is not our intent to give the impression that rumination is a frequent cause of failure to gain weight. The situation described is certainly an exceptional one. But it is by no means rare to find a discrepancy between the amount of food a child is thought to be taking and the amount he actually receives. When accurate records are not kept the impressions about quantities ingested may be very faulty. And when there is regurgitation it is extremely difficult to estimate with any degree of accuracy the caloric loss. A meticulous examination of the intake will often provide the explanation for the calories that have apparently vanished.

Fig. 2.

In conclusion, it may be noted that the paradoxical situation is not infrequently encountered of a child who although apparently receiving adequate calories and with no apparent excessive caloric loss in the excreta fails to gain weight and grow. Examination of a number of such situations has revealed that excreta of quite normal appearance may conceal marked caloric losses. Other instances are explained by failure to ingest the calories actually thought to be ingested or to estimate accurately losses sustained by regurgitation.

REFERENCES

1. Siwe, S.: Considerations on the development of dystrophia infantum. *Acta Paediat.* (Suppl. 100) 43: 575, 1954.

2. Levine, S. Z., Wilson, J. R., and Gottschall, G.: The respiratory exchange in marasmus. *Am. J. Dis. Child.* 35: 615, 1928.
3. Holt, L. E., Jr., Tidwell, H. C., and Scott, T. F. M.: Studies in fat metabolism. I. Fat metabolism in normal infants. *J. Pediat.* 6: 427, 1935.
4. Chung, A. W., Morales, S., Snyderman, S. E., Lewis, J. M., and Holt, L. E., Jr.: Studies in steatorrhea; effect of level of dietary fat on the absorption of fat and other foodstuffs in idiopathic celiac disease and cystic fibrosis of the pancreas. *Pediatrics* 7: 491, 1951.
5. Morales, S., Chung, A. W., Lewis, J. M., Messina, A., and Holt, L. E., Jr.: Absorption of fat and vitamin A in premature infants. I. Effect of different levels of fat intake on the retention of fat and vitamin A. *Pediatrics* 6: 86, 1950.
6. Krahulik, L., Shoob, M. P., Morales, S., Snyderman, S. E., and Holt, L. E., Jr.: Congenital obliteration of the bile ducts with particular reference to dietotherapy. *J. Pediat.* 41: 774, 1952.
7. Holt, L. E., Jr.: Celiac disease—what is it? *J. Pediat.* 46: 369, 1955.
8. Bang, I.: Ueber Lipämie. III. Die Gewöhnung an Fett. *Biochem. Zeitschr.* 91: 112, 1918.
9. Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C.: Physiological effects of diets unusually rich in protein or inorganic salts. *J. Biol. Chem.* 71: 317, 1927.
10. Addis, T., Lee, D. D., Lew, W., and Poo, L. J.: The protein content of organs and tissues at different levels of protein consumption. *J. Nutrition* 19: 199, 1940.
11. Dean, R. F. A., and Schwartz, R.: The effects of protein deficiency in young children. *Courrier* 4: 293, 1954.

Treatment of Severe Protein Deficiency in Children (Kwashiorkor)

By MOISÉS BÉHAR, M.D.,* FERNANDO VITERI, M.D.,† AND NEVIN S. SCRIMSHAW, PH.D., M.D.‡

IT IS NOW well recognized that severe protein malnutrition in children is an almost universal problem in the so-called underdeveloped areas of the world. It occurs most frequently in the young child soon after weaning due to the failure of the parents to introduce proper complementary feeding and to provide an adequate substitute for the protein of breast milk after weaning.

When, despite a lack of adequate protein in the diet, the child receives sufficient calories from sugar and starchy foods, the result is "classic" or "sugar baby" kwashiorkor. Only a very few of the many areas in which protein malnutrition in children is a serious problem report this type; far more frequently there is also an acute or chronic deficiency of calories and the combined deficiency produces the so-called marasmic type of kwashiorkor. The former represents an easier treatment problem since subcutaneous fat is well retained and marked tissue wasting is not present. A diet rich in protein of high biologic value readily cures it without much need for supporting measures.[1]

Neither of the two conditions should be confused with simple starvation or marasmus which represents a different etiopathogenic problem. Marasmus occurs when there is a severe dietary deficiency of both protein and calories; the child does not show the loss of enzyme activity, apathy, and anorexia found when the deficiency of protein is more marked than that of calories. Perhaps the starved child has been living on its own tissues and in this sense has been consuming protein of good quality. At any rate there is increasing evidence that there are important physiologic and biochemical differences between kwashiorkor in any form and classic marasmus.[1] The treatment of the ordinary case of marasmus is essentially the same as that for mild kwashiorkor without serious electrolyte imbalance and will not be discussed further in this paper.

The marasmic form of kwashiorkor is also associated with severe tissue wasting and loss of subcutaneous fat and generally shows dehydration despite the edema.[2–6] Moreover, these cases are likely to have an infection which has helped to precipitate the acute form of the disease. Treatment in these cases becomes a far more complex problem, involving restoration of fluid and electrolyte balance and combat of infection, as well as refeeding. In Central America, as in most other areas in which kwashiorkor is prevalent, the "classic" form is almost never seen. The present paper outlines the management of cases of marasmic kwashiorkor with the observation that in "classic" cases many of the measures indicated may be unnecessary. No detailed description of the characteristics of kwashiorkor is attempted, since these have been adequately reviewed.[7,8] Similarly, the biochemical responses to treat-

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* Associate Director and Head of the Kwashiorkor study project, Institute of Nutrition of Central America and Panama (INCAP), Guatemala, C. A.

† Research fellow, INCAP.

‡ Regional Advisor in Nutrition, Pan American Sanitary Bureau, Regional Office for the Americas of the World Health Organization, and Director of INCAP.

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ment have been reported in detail elsewhere,[9,10] and the problems of prevention extensively discussed.[11,12]

GENERAL MEASURES

Children with kwashiorkor are very susceptible to infection and should be separated from other patients on admission to the hospital to protect them from cross infection. As compared with the recovery of children admitted to a large open ward, the relative isolation provided by individual cubicles in small hospital wards improves the rate of recovery of kwashiorkor patients, even without the introduction of strict isolation technic.[10]

The skin of the child with kwashiorkor is likely to be excoriated and to require good nursing care to control secondary infection of the involved areas. If the child's position is not frequently changed, decubitous ulcers are likely to develop and bronchopneumonia is also a more serious hazard. Since these children are initially extremely apathetic and will ordinarily stay in a position without moving, this must be taken into consideration by the nurses and other ward attendants. These patients are also susceptible to cold and must be kept well covered.

When kwashiorkor patients are given only routine attention by the hospital staff, recovery is much slower than when they can be given special attention. Extreme patience is required on the part of the nursing staff, particularly in the feeding of children during early treatment. These children are usually extremely anorexic and will not ordinarily eat well enough of their own accord for satisfactory recovery.

MEDICAL HISTORY AND PHYSICAL EXAMINATION

The medical history and physical examination must be sufficiently thorough to determine the type and severity of case, character, and degree of dehydration as well as the presence of any kind of infection It is obviously important to know about the possible presence of pneumonia, tuberculosis, meningitis, malaria, amebiasis, infectious diarrhea, contagious diseases of childhood, and other conditions requiring immediate attention if normal recovery is to be obtained. Information as to the medical and dietary history will also be of help in giving instructions to the parents designed to prevent a recurrence after discharge from the hospital.

LABORATORY PROCEDURES

Of immediate practical necessity are assays of serum protein or serum albumin and routine stool, urine, and hematologic examinations. The serum protein or albumin determination gives a general idea of the severity of the protein deficiency and is the most convenient laboratory means for estimating response to treatment. The determination of the urine volume, density, and pH helps to evaluate the dehydration and electrolyte imbalance. Microscopic examination of the urine sediment may reveal a urinary infection which requires prompt treatment. A urine examination will also serve to detect renal disorders which may be responsible for edema. The severity and type of the anemia should be determined as a guide to supplementary therapy. An elevated white-cell count is of little value since even mildly infected cutaneous lesions can be expected to produce a leukocytosis, but the occasional occurrence of leukopenia, even in the presence of frank infection, is a grave sign.

Even without mention of the many laboratory determinations of research interest there are a number of additional procedures of value. In cases with severe dehydration, the determination of urine chloride, of CO_2 combining power in the blood, and of serum chloride and potassium will often lead to a more rational management of the case and may save additional lives, although admittedly these determinations are not ordinarily available where kwashiorkor is a major problem. Either pseudo-cholinesterase or serum amylase can be profitably followed as a further measure of recovery, although each gives essentially the same information with ordinary therapy as the serum protein.

The stool examination should indicate the presence or absence of amebiasis so that this complication may be treated immediately. Stool culture for the identification of pathogenic bacteria may be of value since Shigellosis

should also receive prompt and effective treatment. Because routine antibiotic administration is recommended, radiographic examination of the chest is not considered essential. However, bronchopneumonia is a frequent cause of early death in kwashiorkor and it is often virtually impossible to detect it by physical examination alone.[13,14] A radiograph of the chest gives added confidence when bronchopneumonia is shown not to be present and encourages additional caution when it is found. It is also desirable for the detection of the not infrequent case in which pulmonary tuberculosis is a serious complication. For this reason also, a tuberculin test during the child's hospital stay is indicated, although the possibility of a false negative skin reaction in severe malnutrition makes it unreliable until substantial recovery has occurred.[15]

INITIAL THERAPY

The problem of severe dehydration and electrolyte imbalance has long been studied in connection with diarrheal disease. There is the further complication, however, that protein malnutrition alone, even in the absence of diarrhea, produces a deficiency of potassium and an imbalance of other electrolytes with an accompanied shift in the content of the fluid compartments.[16–18] It is increasingly recognized that a major problem in the early management of kwashiorkor is the correction of the often severe dehydration and electrolyte imbalance found on admission, but there are few detailed studies to serve as a guide to rational therapy. We would suggest the following procedures.*

Mild Electrolyte Imbalance

(Frank kwashiorkor with no clinical signs of dehydration; no vomiting; diarrhea not severe.)

In very mild cases adding sufficient potassium chloride to provide a total of 4 to 6 meq of potassium per body weight daily is sufficient. One gram of potassium chloride provides 13.4 meq and whole milk contains about 40 meq per liter.

In ordinary mild cases, we find it convenient for the first two to three days to add the major anions and cations in appropriate proportions to the milk formula, the amounts depending on the clinical condition of the child.* At the end of this time the electrolytes of the normal diet are sufficient to complete the correction of any remaining imbalance. In some of these children who present marked abdominal distention, it is desirable to increase the potassium intake, if adequate diuresis is present, by the direct addition of potassium chloride to the salt mixture incorporated in the milk formula. The total amount of potassium recommended is in the range of 10 to 12 meq per kg daily. This is on the assumption that less than half the ingested potassium may be absorbed in some cases and that the average absorption is not greatly over this.

Moderate and Severe Electrolyte Imbalance

(Kwashiorkor with marked clinical signs of dehydration).

(a) *Associated with Moderate to Severe Diarrhea:* The basic problem is severe dehydration, hyperosmolarity, metabolic acidosis, and multiple anion and cation loss, especially of potassium. As soon as possible after admission, the child should be given a buffered hypotonic solution intravenously to counteract the acidosis and hyperosmolarity as well as begin the correction of the dehydration and oliguria. If laboratory facilities for determining CO_2

* In the preparation of this Section we have been greatly aided by the information presented at a Symposium entitled *Seminario sobre Desequilibrio del Agua y Electrolitos* by Drs. F. Gómez, J. Cravioto, S. Frenk, G. Gordillo, and R. Ramos Galván at the III Congreso Centroamericano de Pediatria y VII Congreso Nacional de Medicina held in Guatemala, November, 1956.

* We have generally used 40 to 80 g of Lytren® (Mead Johnson & Co.), of which 80 g provides the following meq: sodium, 50, potassium, 20, calcium, 4, magnesium, 4, citrate, 50, sulfate, 4, chloride, 30, phosphate, 10, and lactate, 4.

When suitable commercial preparations are not available, the following mixture will prove satisfactory: Lemon juice, 100 ml, $CaCO_3$, 0.5 g, NaCl, 0.5 g, KCl, 2.0 g, $NaHCO_3$, 4.2 g, sugar, 50 g, water to 1,000 ml. It will provide the following meq: Na^+, 59; K^+, 27; Ca^{++}, 10; Cl^-, 35; citrate^{---} 78. The dosage is 120 to 200 cc per kg given in frequent small amounts throughout the day varying with the state of hydration.

combining power and serum electrolytes are not available, this therapy must depend on clinical observation and experience.

We recommend a so-called 1-2-3 solution* of one part of $^1/_6$ molar sodium lactate, two parts of Ringer's solution,† and three parts of 5 per cent glucose. The lactate in this solution combats the acidosis, the glucose diminishes the ketosis and the Ringer's solution, which contains 6 meq of calcium and 4 meq of potassium per liter, helps to correct the hypocalcemia and potassium depletion. The dosage varies from 40 to 50 cc per kg‡ administered intravenously at a rate of 40 to 50 drops per minute.

In most cases diuresis begins after the preceding treatment has been administered. (If not, the solution can be continued some hours longer if a slower rate is employed.) It is then advisable to continue with Darrow's solution§ more slowly, approximately 20 to 25 drops per minute at a dosage of 90 to 110 cc per kg per day, and to give additional 5 per cent glucose in either normal saline or Ringer's solution to help replace the total water loss. It is usually necessary to give between 150 and 200 cc of fluid per kg in the first 24 hours. Close and frequent examination is required to guide this therapy, since clinical signs and the diuresis are the best indices of the amount required. Oral feeding should begin as soon as the patient's condition permits, often within a few hours after admission.

(b) *Associated with Moderate to Severe Vomiting as well as Diarrhea:* These cases are rare, but may present a slightly different problem due to the loss of hydrochloric acid from the stomach and the superimposition of metabolic alkalosis on the fluid and electrolyte disturbances discussed previously. If vomiting has been sufficiently acute to produce alkalosis, the sodium lactate is omitted from the solution given. The remainder of the treatment is essentially the same.

It is important, however, to point out that in children suffering from edema, especially when this condition is associated with dehydration through diarrhea and/or vomiting, derangements of the fluids and electrolytes equilibrium are very complicated and not yet clearly understood. Consequently these imbalances are difficult to correct. Metcoff *et al.*[19] have found hypotonicity associated with intracellular edema and suggest the possibility of successful use of hypertonic solutions in these cases. We feel, however, that the use of such solutions has not been as yet critically studied and it might well be that it may prove dangerous in some instances.

Use of Antibiotics and Chemotherapy

Even when infection is not initially present, the susceptibility to infection of the child with kwashiorkor is so great that routine antibiotic therapy is recommended. It is important to realize that in severe kwashiorkor neither fever nor elevated white-cell count may develop, even when the infection is severe; the child seems to lose his ability to respond to infection in these classic ways. Our experience suggests that a high percentage do have infection present even though it may not be obvious upon initial clinical examination. This is particularly true for bronchopneumonia which is a frequent autopsy finding even when clinically undetected.[13,14]

It is our practice to give 600,000 to 1,200,000 units of crystalline penicillin daily intramuscularly every four hours for at least the first 24 hours, and then change to long-acting penicillin in a doses of 300,000 to 600,000 once daily for six to eight days.

We have not tried "broad-spectrum" antibiotics because of their known tendency to produce diarrhea and/or vomiting in children, and because of the theoretic possibility of encouraging fungus infections and staphylococcal di-

* If facilities are not available for preparing this solution, the Ringer-lactate solution of Hartmann can be used, which, however, supplies less lactate. It contains per 1,000 ml: NaCl—6.0 g, KCl—0.3 g, $CaCl_2$—0.2 g, and Na lactate—3.1 g.

† Although normal (0.9 per cent) saline can also be employed, Ringer's solution is better. It contains per 1,000 ml: NaCl—8.5 g, KCl—0.3 g, and $CaCl_2$—0.2 g.

‡ Many authors advocate the technically more correct procedure of calculating dosage on a surface area basis. With the abnormal weight relations in kwashiorkor due to edema and marasmus and the variation in appropriate dosage with the individual, we doubt whether this extra step is justified.

§ Darrow's solution contains per 1,000 ml: NaCl—3.0 g, KCl—2.7 g, and $NaHCO_3$—4.4 g.

arrhea. Both chloramphenicol and sulfadiazine have been used routinely by other authors.

If either malaria or amebiasis are diagnosed, specific therapy is given at once. Similarly, when acute bacillary dysentery due to *Shigella* can be specifically identified, sulfadiazine or chloramphenicol is given.

Initial Diet

It is of general practice to give half-skim milk, although most of the African workers have used skim milk in the early treatment of kwashiorkor,[20,21] and the successful use of whole milk has been reported from Mexico.[22] When either half-skim or whole milk is used, the diarrhea is better controlled if the milk is acidified to produce a finer curd.* Half-skim milk gives a slightly higher fat and calorie intake without significant reduction in the protein. Not only is there no contradiction to a moderate fat intake in either diarrhea in general or the diarrhea of kwashiorkor in particular, but on the contrary, the inclusion of fat in the therapeutic diet for these conditions has been strongly recommended.[23,24]

For the first 24 hours we employ the milk diluted with water to half strength but with 5 per cent sugar added and give either 120 cc every two hours (eight times a day) or, if not well tolerated, 60 cc every hour (16 times a day). If large single volumes are given, there is a risk of producing an acute dilatation of the stomach or of provoking vomiting. Not infrequently, it is necessary to resort to gastric intubation due to the extreme anorexia of the child and inability of the nurse to persuade him to accept sufficient formula. With the use of a polyethylene tube we have encountered no complications from this procedure, and the tube can be left in place for several days, if necessary. This initial diet supplies only 1 to 2 g of protein and 30 to 60 cal per kg during the first 24 hours.

If it is well tolerated, the concentration should be increased to three-quarters strength during the second 24 hours and to full strength by the third or fourth day. In the meantime, the amount of formula given is increased as rapidly as tolerated to 180 cc every three hours six times daily, and then to 240 cc at the same intervals five times daily, so that the child is receiving approximately five g of protein and 100 cal per kg by the fourth to sixth day. If the child will accept solid food, it is desirable to give half a banana twice a day as early as the second or third day as a source of well-tolerated calories which does not increase the diarrhea. If the child is hungry he can soon be given a whole banana twice a day. While we have utilized calcium caseinate without difficulty, as recommended by Dean,[25] we have abandoned its use because the foregoing regimen alone has given an adequate response.

* Six cc of lactic acid or 20 cc of lemon juice added drop by drop to 1,000 cc of the milk with constant stirring.

Role of Plasma and Blood Transfusion

Whole blood transfusion is widely recommended and employed for the initial treatment of severe kwashiorkor. As our experience with the management of these cases has grown, we have come to use transfusion very rarely, and now believe that except for severe anemia, it is indicated only when the child's life seems in danger from collapse or shock produced by severe dehydration or toxicity due to infection. In these cases blood or plasma should be considered a necessary part of the treatment scheme. Usually 10 to 20 cc of whole blood per kg is sufficient or, if not available, 20 to 30 cc per kg of plasma can be given. Larger transfusions can cause too fast a loss of edema with more rapid circulatory changes than the child can tolerate. As protein sources, neither plasma nor intravenous or oral protein hydrolysates are necessary or justified.

Role of Enzyme and Lipotropic Preparations

Despite the reduced duodenal enzyme activity in kwashiorkor, milk protein is satisfactorily absorbed from the beginning,[26,27] and enzyme recovery is very rapid.[10,28] There is no reason to believe that the administration of enzyme preparations will have a significant effect on promoting recovery. Much the same comment applies to the various lipotropic preparations recommended. Liver fat disappears rapidly with milk treatment alone and we regard the supposed advantages of adminis-

tering methionine and choline preparations as unsubstantiated.

FURTHER TREATMENT

During the second week of therapy whole non-acidified milk is gradually introduced and the amount increased to supply approximately 7.0 g of protein per kg. With two bananas a day and 120 cc of orange juice, the total calories are brought to approximately 130 per kg. During the second or third week of hospitalization, green and yellow vegetables are added. During the third or fourth week, depending upon the appetite and progress of the child, meat, eggs, cereals, and bread are added. At the end of one month of hospitalization the child should receive a varied and balanced diet which contains all necessary vitamins and minerals in physiological amounts. By this time the protein intake should average 5.0 to 6.0 g per kg and the caloric intake 140 to 150 per kg.

At the time of admission some of the children with kwashiorkor show a microcytic hypochromic anemia due to iron deficiency. The remainder have a normocytic or macrocytic anemia which very frequently becomes microcytic as treatment proceeds because iron becomes limiting.[10] The therapeutic diet suggested above, although adequate to supply ordinary iron requirements, does not replete iron reserves sufficiently rapidly for optimum hematologic response. We therefore recommend the oral administration of iron in a dosage of 300 mg of ferrous sulfate once or twice daily depending upon the severity of the anemia. This should be started during the second week or as soon thereafter as diarrhea stops and is usually, but not always, well received. A suitable preparation of iron for intramuscular administration would seem appropriate for use wherever oral therapy is not well tolerated, although we have not had personal experience with it.

When ocular lesions are present, it is wise to give supplementary vitamin A daily from the time of admission. No other supplementary vitamins need be given either parenterally or orally, even if the child presents signs suggesting other specific vitamin deficiencies. There is evidence that early vitamin B-complex administration in high doses may be distinctly harmful.[29] After satisfactory recovery has taken place, the child should receive adequate treatment for such intestinal parasites as may be present.

VEGETABLE PROTEIN MIXTURE

There is sufficient evidence to conclude that a properly selected and prepared mixture from vegetable protein sources can be used for the treatment of kwashiorkor.[12,25,30,31] These studies have had as their object the testing of vegetable protein combinations to be used for the prevention of kwashiorkor and do not necessarily represent the most convenient method of treatment. Nevertheless, where adequate supplies of milk are not available, there is no reason why vegetable mixtures may not also be used. The difficulty lies only in being sure that the particular combination available is really safe and effective.

PSYCHOLOGIC FACTORS IN RECOVERY

At the time of admission the child is generally profoundly apathetic and anorexic and when aroused is hyperirritable. He has generally arrived at this state after a long period of neglect and frustration.[32,33] It is important from the beginning to try to give the child attention and to treat him sympathetically and with understanding. An effort should be made to arouse the interest, curiosity, and sociability which should characterize children of this age. In general, these children are backward in their psychomotor development. Attention to their speech, walking, and play brings about better cooperation with the therapeutic regime and more rapid recovery. Cheerful surroundings and a friendly attitude on the part of the staff as well as the provision of a few toys and a play area mean a great deal.

PREVENTION OF RELAPSES

The prevention of a relapse begins when the child is given a balanced diet and learns to accept green and yellow vegetables, meat, eggs, and other components of a varied diet. Advantage should be taken of the visits of the parents to explain to them the purely dietary nature of the treatment and the fact that a poor diet was responsible for the development

of the disease in their child. The parents can usually be convinced of the necessity of giving the child an improved diet after its discharge from the hospital. In our own experience at least, recurrences are not only very rare when there has been an opportunity to indoctrinate the parents, but also the child on successive follow-up visits is frequently in better physical condition than other children of the same age in the neighborhood.

Whenever possible, arrangements should be made for the child to be brought back at regular intervals for re-examination, preferably monthly for the first three to six months and quarterly thereafter. This gives a further opportunity to check on the diet provided by the parents and to give additional instruction to them. An opportunity is often presented at this time for examination of other children in the family and for giving advice on their care and on the better use of the family income for food purchases. Much can also be gained if the parents can be persuaded to continue giving a good diet, even if diarrhea should develop. The customary withdrawal of solid food and administration of purgatives in such an event poses a constant threat to the recovered child.

GENERAL COMMENTS

The recommended treatment of uncomplicated but severe protein malnutriton (kwashiorkor) in children without pronounced diarrhea is almost entirely dietary. The principles of treatment of this syndrome are summarized in Table I. The problems of initial management derive from complications such as diarrhea, water and electrolyte imbalance, and infection, and from the usual but not invariable accompaniment of a significant degree of marasmus. Acute vitamin-A deficiency and severe anemia may also be associated problems. Detailed suggestions for handling these complications and related deficiencies have been given, but the general problems of hospital care should be mentioned further.

The child is particularly susceptible to both respiratory and enteric infections and should be protected from these as much as is practical, as well as from the contagious childhood diseases;

TABLE I

Summary of the Therapeutic Regimen Recommended for Kwashiorkor (Marasmic Type)

	First 24 hours	Second to fourth day	First to second week	Second to fourth week	Convalescence
Fluids and electrolytes	Electrolyte imbalance, Mild: Electrolyte solutions orally Moderate to severe: intravenous electrolyte solutions	Electrolytes or K added to formula Continue intravenous electrolyte solutions	K added to the formula if necessary	—	—
Antibiotics	Crystalline penicillin, 600,000–1,200,000 units/day	Long-acting penicillin, 300,000–600,000 units/day	Long-acting penicillin, 300,000–600,000 units/day	—	—
Proteins g/kg/-day	1-2	2–5	5–7	5–7	5–6
Calories kg/day	30–60	60–100	100–130	130–150	140–150
Ferrous Sulfate orally mg/day	—	—	300–600	300–600	300–600
Diet	Half-skim acidified milk, half-strength	Half-skim acidified milk 3/4 to full strength	Whole milk plus banana, orange juice, vegetables	Same plus meat, eggs, cereals	Balanced high protein-high calorie diet

infections of any kind are likely to retard recovery and may endanger the life of the child. Often a small hospital unit can do a better job than a large one since the facilities required for treatment are not specialized and the child is likely to receive more individual attention and less exposure to cross infection in the former. Figure 1 portrays the complete recovery possible with the treatment recommended.

Careful attention to the details of the therapeutic regimen outlined will result in large savings to hospital administrators. Routine blood transfusion, parenteral vitamins, enzymes, and amino-acid preparations are expensive and quite unnecessary; eliminating their use can result in substantial savings. Even more important is the cost of prolonged hospitalization. The duration of hospitalization in the Guatemala General Hospital has been found to be much longer than for cases treated under our supervision in a nearby well run hospital under the auspices of a private charity. Furthermore, the condition of the children at the time of discharge from these private hospitals is consistently better despite the shorter treatment period. We believe that the more favorable response of children in the private institutions was due to a combination of more attention to the diet actually consumed by the child, reduced exposure to secondary infections, and more concern for surroundings and the psychologic aspects of care.

Although beyond the formal scope of this paper, better outpatient care could reduce the number of cases requiring hospitalization. Cursory dietary instructions to the mother, which are beyond both her comprehension and economic resources, are of little value. Even worse is the treatment of diarrhea by the physician without any attention to the early or distinct signs of malnutrition which may be present in the patient. In some areas of the world most children in lower economic groups are in a state of pre-kwashiorkor; in these children diarrhea may have serious consequences and often leads to the development of outright kwashiorkor. The prevention and proper management of diarrhea thus play an important part in prophylaxis.

The prophylaxis of kwashiorkor cannot be left to public-health workers alone; physicians charged with outpatient care should help to prevent hospitalized cases by realistic dietary instructions to parents with malnourished children. They should also see that children attending outpatient clinics who develop kwashiorkor are hospitalized before they develop dangerous therapeutic complications which require costly and prolonged hospital treatment.

Fig. 1. A 17-month-old boy is shown on the left at the time of his admission to the hospital with moderately severe kwashiorkor and at the right at the time of discharge from the hospital. Good recovery took place in this child in 5 weeks.

SUMMARY

Detailed suggestions for the treatment of children with severe protein malnutrition (kwashiorkor) are given. These include attention to the fluid and electrolyte imbalances which are likely to characterize the acute case due to secondary complications and instructions for beginning treatment with frequent feedings of milk diluted to half strength. One to 2 g of protein and 30 to 60 cal per kg are given in the first 24 hours and the strength and amount of milk increased to provide 5 g of protein and 100 cal per kg by the end of the first week. Bananas, fruit juice, meat, eggs, vege-

tables, and cereals are gradually added to give a diet throughout most of the recovery period containing 5 to 7 g of protein and 130 to 150 cal.

Penicillin is given routinely for the first eight to ten days and supplementary iron therapy is started after one week has elapsed. Vitamin A is given when serious ocular lesions are present and whole blood transfusion may be necessary in the rare case of collapse, shock, or severe anemia; no other vitamins or minerals and no special enzyme or lipotropic preparations are indicated. The importance of protection from infection and the need for sympathetic and understanding care are stressed. The cost of hospitalization of kwashiorkor cases can be drastically reduced by eliminating the use of costly proprietary preparations and by greatly shortening the hospital stay through close attention to the principles of treatment described.

REFERENCES

1. JELLIFFE, D. B., BRAS, G., and STUART, K. L.: Kwashiorkor and marasmus in Jamaican infants. *West Indian Med. J.* 3: 43, 1954.
2. BROCK, J. F., and AUTRET, M.: Kwashiorkor in Africa. *FAO Nutritional Studies No. 8*, Rome, Italy, 1952. *WHO Monograph Series No. 8*, Geneva, 1952.
3. VAN DER SAR, A.: Incidence and treatment of kwashiorkor in Curacao. *Docum. Neerl. et Indonés. Morbis Tróp.* 3: 25, 1951.
4. GOPALAN, C.: Kwashiorkor in Uganda and Coonoor (A comparison of some salient aspects). *J. Trop. Pediatrics* 1: 206, 1956.
5. DEMAEYER, E. M., and VANDERBORGHT, H.: Evolution de la courbe pondérale et de certains contituants biochimiques et hématologiques du sang dans le kwashiorkor. *Ann. Soc. Belge Méd. Trop.* 34: 417, 1954.
6. AUTRET, M., and BEHAR, M.: *Sindrome Policarencial Infantil (Kwashiorkor) and Its Prevention in Central America.* FAO Nutritional Studies No. 13. Food and Agriculture Organization of the United Nations, Rome, 1954.
7. TROWELL, H. C., DAVIES, J. N. P., and DEAN, R. F. A.: *Kwashiorkor*, ed. 1, Edward Arnold, London, 1954.
8. SCRIMSHAW, N. S., BEHAR, M., ARROYAVE, G., VITERI, F., and TEJADA, C.: Characteristics of kwashiorkor (sindrome pluricarencial de la infancia). *Fed. Proc.* 15: 977, 1956.
9. DEAN, R. F. A., and SCHWARTZ, R.: The serum chemistry in uncomplicated kwashiorkor. *Brit. J. Nutrition* 7: 131, 1953.
10. SCRIMSHAW, N. S., BEHAR, M., ARROYAVE, G., TEJADA, C., and VITERI, F.: Severe protein malnutrition (kwashiorkor) in children and its response to protein therapy. *J. A. M. A.* 164: 555, 1957.
11. SCRIMSHAW, N. S., BEHAR, M., VITERI, F., ARROYAVE, G., and TEJADA, C.: Epidemiology and prevention of severe protein malnutrition (kwashiorkor) in Central America. *Am. J. Pub. Health* 47: 53, 1957.
12. BEHAR, M., VITERI, F., BRESSANI, R., ARROYAVE, G., SQUIBB, R. L., and SCRIMSHAW, N. S.: Principles of treatment and prevention of severe protein malnutrition in children (kwashiorkor). *Ann. New York Acad. Sc.*, 1957. (To be published.)
13. GOMEZ, F., RAMOS GALVAN, R., FRENK, S., CRAVIOTO, M. J., CHAVEZ, R., and VASQUEZ, J.: Mortality in second and third degree malnutrition. *J. Trop. Pediatrics* 2: 77, 1956.
14. TEJADA, C., BEHAR, M., and CONFIÑO, E.: Estudio clínico patologico de las bronconeumonías en el niño desnutrido. *Revista del Colegio Médico de Guatemala* 7: 134, 1956.
15. KOLMER, J. A.: *Clinical Diagnosis by Laboratory Examinations.* ed. 2. Appleton-Century-Crofts, New York, 1949.
16. HANSEN, J. D. L., and BROCK, J. F.: Potassium deficiency in the pathogenesis of nutritional oedema in infants. *Lancet* 2: 477, 1954.
17. CANNON, P. R., FRAZIER, L. E., and HUGHES, R. H.: Sodium as a toxic ion in potassium deficiency. *Metabolism* 2: 297, 1953.
18. THOMPSON, M. D.: Potassium deficiency and kwashiorkor. *Lancet* 2: 1181, 1955.
19. METCOFF, J., JANEWAY, C. A., GAMBLE, J. L., FRENK, S., GORDILLO, G., RAMOS GALVAN, R., and GOMEZ, F.: Hypotonicity and intracellular edema in severe chronic malnutrition with recurrent diarrhea. *A. M. A. J. Dis. Child.* 92: 462, 1956.
20. TROWELL, H. C.: Clinical aspects of the treatment of kwashiorkor. *Ann. New York Acad. Sc.* 57: 722, 1954.
21. RAOULT, A.: Clinical aspects of kwashiorkor in French West Africa. Malnutrition in African mothers, infants and young children. *Report of Second Inter-African (C. C. T. A.) Conference of Nutrition.* Gambia, 1952, H. M. S. O., London, 1954, p. 37.
22. GOMEZ, F.: Personal communication. December, 1956.
23. HOLT, L. E., JR.: Algunas reflexiones sobre el problema de la deficiencia severa de proteínas en los niños. *Memorias del II Congreso Centro Americano de Pediatría.* San Salvador, 1954.
24. DEAN, R. F. A.: Advances in the treatment of kwashiorkor. *Bull. World Health Organ.* 14: 798, 1956.
25. DEAN, R. F. A.: Treatment and prevention of

kwashiorkor. *Bull. World Health Organ.* 9: 767, 1953.

26. HOLEMANS, K., and LAMBRECHTS, A.: Nitrogen metabolism and fat absorption in malnutrition and in kwashiorkor. *J. Nutrition* 56: 477, 1955.
27. BEHAR, M., ARROYAVE, G., TEJADA, C., VITERI, F., and SCRIMSHAW, N. S.: Desnutrición severa en la infancia. *Revista del Colegio Médico de Guatemala* 7:221, 1956.
28. VEGHELYI, P.: Activité pancréatique et carence des protides. *Acta Chir. Belg.* supp. 2, p. 374, 1948.
29. MAGALHAES CARVALHO, J. DE: Contribuicao ao tratamento da distrofia pluricarencial hidropigénica. *Hospital, Río de Janeiro* 32: 307, 1947.
30. SCRIMSHAW, N. S., SQUIBB, R. L., BRESSANI, R., BEHAR, M., VITERI, F., and ARROYAVE, G.: Vegetable protein mixtures for the feeding of infants and young children. In *Amino Acid Malnutrition. XIII Annual Protein Conference*, Rutgers University Press, 1957.
31. GOMEZ, F., RAMOS GALVAN, R., BIENVENU, B., and CRAVIOTO MUÑOZ, J.: Estudios sobre el niño desnutrido. X. La recuperación del niño desnutrido, empleando proteínas de origen vegetal y proteínas de origen animal. Informe de 3 experiencias comparativas. *Bol. Médico del Hosp. Inf.* 9: 399, 1952.
32. GOMEZ, F., VELASCO ALZAGA, J., RAMOS GALVAN, R., CRAVIOTO, J., and FRENK, S.: Estudio sobre el niño desnutrido. XVII. Manifestaciones psicológicas; comunicación preliminar. *Bol. Médico del Hosp. Inf.* 11: 631, 1954.
33. GEBER, M., and DEAN, R. F. A.: Psychological factors in the etiology of kwashiorkor. *Bull. World Health Organ.* 12: 471, 1955.

Iron and Copper in Infant Nutrition

By M. EUGENE LAHEY, M.D.*

IRON and copper are appropriately discussed together for several reasons, chief of which is that the importance of physiologic interactions between the various trace elements was first recognized during the course of investigations involving these two metals. In experiments, now well known, Elvehjem and coworkers[1] demonstrated that the anemia occurring in weanling rats fed nothing but milk responded to purified iron salts only when copper was provided. Because these findings were especially attractive to physicians caring for infants, it seems all the more appropriate that iron and copper be discussed together here. No attempt will be made, however, to review the metabolism of either exhaustively, nor to include a discussion of their potential toxic effects. Rather, this paper deals with those features of iron and copper in nutrition which are of special interest and importance to the physician concerned with the care of healthy and sick infants. More complete reviews are available.[2-6]

IRON

It is indeed discouraging when it is realized that the incidence of iron-deficiency anemia in this hospital and clinic appears to have remained unchanged during the past 20 years,[7] a period during which the incidence of other nutritional deficiencies was very substantially reduced. Yet, anemia due to a deficiency of iron continues to account for almost 50 per cent of anemic patients of all ages admitted to this children's hospital,[8] and it occurs with astounding frequency in the very young. Approximately 25 to 30 per cent of infants between 6 and 24 months old who are hospitalized have less than 10.5 g of hemoglobin per 100 ml blood; in about 90 per cent of these the anemia is due to iron deficiency. Evidence has also been presented which indicates that even in infants deemed "healthy" and "normal" by currently accepted hematologic standards, certain biochemical changes considered pathognomonic of tissue iron depletion are usually found. Thus, a reduction in the serum iron, and elevations in values for the iron-binding capacity of serum as well as for serum copper and erythrocyte protoporphyrin, indicate that subclinical or marginal states of iron deficiency are common in this age group.[9]

PATHOGENESIS OF IRON DEFICIENCY

Such a high incidence of anemia and of marginal deficiency is not surprising when one recalls that per unit of body weight, the requirement for iron for incorporation into hemoglobin is two to three times greater during the first two years of life than at any other period.[10] Needs are still greater in the prematurely born. In addition to requirements for growth of the hemoglobin compartment, there are also increased needs for other iron-containing compounds, e.g., myoglobin and the cytochrome enzymes. At present, however, the magnitude of these extra-hemoglobin requirements for iron can only be estimated at 4 to 7.5 mg/kg of body weight.[3,11] Their importance relative to the incidence of anemia is not clear, although they seem to enjoy a higher priority than does hemoglobin.

Whenever the amount of iron available from tissue "stores" and from the dietary intake fails to meet the total iron requirements, iron deficiency results. The explanation for differing degrees of anemia in two infants of the same age and with similar rates of growth lies, therefore, predominantly in the differences in avail-

From the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio.

* Associate Professor of Pediatrics, University of Cincinnati College of Medicine and Supervising Hematologist, The Children's Hospital, Cincinnati, Ohio.

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able stores and differences in the dietary intake or efficiency of absorption of food iron. The loss of iron, however, cannot be completely ignored. Each of these factors will be considered separately.

Other factors may be operative in the pathogenesis of iron depletion. It has been suggested that hypoferric anemia in infants is not always due to iron depletion but to internal derangements in the metabolism of iron.[12] The role of anxiety, fear, and other emotional disturbances, as well as the role of naturally occurring pyridoxine deficiency, requires further study. The role of copper deficiency will be discussed subsequently. Reasons for believing that infection *per se* seldom does more than aggravate a pre-existing iron-deficient state have already been presented.[8]

Iron Stores: Compared with the adult, who can draw on hepatic stores of iron to tide him over a period of critical need, the newborn is less fortified. In some fetal livers as little as 11.5 mg of iron is found,[13] an amount capable of yielding no more than 3.5 g of hemoglobin. Although two to three times this amount may be found in the liver of other newborn infants, his "stores" reside largely in the hemoglobin compartment. Available data suggested that total blood volume and total body hemoglobin may vary rather markedly from one newborn to another.[11] Obviously, the infant who begins life with a low total body iron is immediately at a disadvantage and must obtain additional iron from dietary sources if anemia is to be prevented. Because of limitations both in the amount of iron present in the infant's food and in its availability, such a disadvantage may be insurmountable.

Several factors that govern the newborn's total body iron are known. The infant born prematurely, for example, may have relatively small stores of iron because of his relatively small blood volume. The practice of early clamping of the umbilical cord deprives the newborn of approximately 30 or 40 mg of iron. At about 12 months of age infants so deprived exhibit a slight but significantly greater degree of anemia compared with those in whom maximal placental transfusion has been permitted.[14] Any loss of the infant's blood at the time of birth would certainly have a depleting effect on the total body iron. Although such loss is usually obvious and ordinarily small in amount, significant amounts of blood may be lost and may go unrecognized. Thus, laceration of placental vessels may occur, an infant may bleed into the mother, or one twin may bleed into the other.[15,16]

Whether the newborn's iron stores are dependent on the maternal iron stores is still debated. The positive evidence would seem better than the negative. Thus, it has been shown that the degree of anemia at about one year of age is greater in infants born to anemic mothers than in those born to nonanemic ones,[17] that anemia becomes more severe in successive infants of the same iron-deficient mother,[18] and that "first born" infants of different mothers are usually less anemic than those "later born."[7] Also the previously cited high incidence of iron deficiency during infancy may be a reflection of the high incidence of this type of anemia during pregnancy.[19] The relationship between maternal and fetal iron stores deserves further study, however, since no correlation between anemia in the mother and its subsequent appearance in the infant was found in a survey involving several hundred women and their offspring.[20]

It is apparent from the study of Smith and co-workers,[21] in which infants thought to have iron-deficiency anemia were excluded, that the amount of iron in the liver is also very small during the late months of infancy. It is possible to calculate from the data presented, using 345 g as an approximate mean weight of the liver, that the total liver iron in infants from 12 to 24 months of age averages only 12 mg and ranges from 10 to 24 mg. This amount would be of little value should the infant's requirement for iron be increased by blood loss or by an inadequate intake of iron.

Dietary Iron: Knowing that the average infant begins life with a total body iron content of about 300 mg[13] and reaches adulthood with 3 to 5 g, one can calculate that about 0.5 mg of iron must be retained each day for 20 years if anemia is to be prevented. Knowing also that the absorption of food iron is poor,[2] one can further calculate that the diet should

contain five to ten times this amount. Furthermore, since studies show that infants up to three or four months of age may be in negative iron balance even while receiving a liberal diet[22] and that dietary iron contributes but little to the infant's hemoglobin during this period,[23] it seems clear that more than 2.5 to 5 mg of iron should be included in the diet of the older infant. A diet of milk alone falls far short, supplying as it does only about 1.5 mg of iron per quart.

Tables presenting the iron content of various foods may be consulted for the construction of an "adequate" diet. Such information, however, is of limited value, since disparity exists between the total amount of iron present in food, the amount of iron chemically available, and the amount of iron physiologically available. Thus, a food of high-iron content may not necessarily be a good source of biologically available iron. Also its availability may be altered by the presence in the diet of items enhancing absorption (ascorbic acid, sulfhydryl groups, etc.) or inhibiting absorption (excess phosphates, phytic acid, etc.). The many factors influencing iron absorption have recently been reviewed.[24] Nevertheless when such tables are consulted, sample diets as recommended in various texts on infant feeding for the 6-or 12-month old baby can be shown to contain amounts of iron consistent with the recommended requirement[2] of 1 mg/kg/day (see Table I). The major contribution to the iron content of such diets is obviously made by enriched cereals, meats and eggs. Lacking these items, the recommended allowances will not be met. However, since the needs for iron and probably the efficiency of absorption vary from one infant to another,[23] it must not be assumed that an "adequate" diet will prevent all hypoferric anemia. Indeed, Brokaw[25] failed to find that the early introduction of cereal, vegetable and eggs had any significant effect on hemoglobin levels during the first year. It must not be assumed either that if already partially depleted of iron, the infant will absorb more food iron to satiate his needs. Although medicinally prescribed iron is better absorbed by the anemic than by the non-anemic subject, the absorption of iron from food may not be any more efficient in the anemic than in the non-anemic subject.[26]

Even though the critical role played by the diet is apparent, to attribute all hypoferric anemia in infancy to a faulty diet and to depend solely on dietary iron for the prevention or cure of iron deficiency is an unjustified oversimplification of available evidence.

Iron Loss: It is known that the iron liberated after the death of erythrocytes is tenaciously conserved and preferentially re-utilized for new hemoglobin synthesis. It has been assumed, therefore, that the problem of iron loss, except as shed blood, can be ignored. Yet some iron loss does occur in the sweat, urine and bile, with the desquamation of skin and mucous

TABLE I

Iron and Copper Content of Sample Diets Consumed by 6- and 12-Month Old Infants*

Food	6 Months			12 Months		
	Amount *g*	Iron *mg*	Copper *mg*	Amount *g*	Iron *mg*	Copper *mg*
Orange juice	75	0.25	0.02	100–150	0.33–0.5	0.03–0.05
Cereal	30–75	3.0–7.5	0.19–0.48	60	6.0	0.38
Fruit	45–60	0.36–0.48	0.04–0.05	60	0.48	0.05
Vegetable	15–30	0.13–0.27	0.03–0.07	30	0.27	0.07
Egg	30	1.2	0.02	54	1.30	0.14
Meat	30	0.74	0.05	30	0.74	0.05
Potato	—	—	—	30	0.18	0.03
Bread	—	—	—	12–23	0.2–0.4	0.03–0.05
Butter	—	—	—	5	—	0.002
Total	—	5.7–10.4	0.35–0.69	—	9.5–9.9	0.78–0.82

* Kindly prepared by Miss Mary S. Breese, Department of Dietetics, Children's Hospital, Cincinnati, Ohio.

membranes, and with the growth of hair. In the adult male, the combined excretion by all routes averages about 1.0 mg per day.[26] Perhaps the small amount lost is inconsequential to the growing infant as it is to the adult male. However, it has been stated that infants under two months of age lose an average of 1.25 mg iron per day.[27] Though this amount seems excessive, it indicates a need for more knowledge of iron loss in infancy, and suggests that this problem should not be excluded as a contributing factor in hypoferric anemia of infancy.

Effects of Iron Deficiency

The clinical and hematologic effects of a deficiency of iron are generally well known; lengthy repetition here would be redundant. Only certain features especially pertinent will be summarized here.

Since the infant does not express complaints of fatigue, palpitation, sore tongue or dysphagia as does the adult, and since the anemia is usually mild in degree and insidious in onset, compensatory adjustments are often nearly complete. Even moderately severe anemia often goes unrecognized by parents and physicians alike, so that it is first discovered only when some associated illness is being investigated. The severely anemic infant, however, is usually extremely irritable and listless and has a striking distaste for foods other than milk. Pica is frequent and potentially dangerous, should the affected infant's environment include such noxious chemicals as lead.

The frequency with which slight hepatosplenomegaly is noted is approximately the same as in the adult, i.e., 10 to 30 per cent.[28] It has been stated that the infant, like the adult, exhibits no evidence of growth failure, but, on the contrary, is often somewhat obese. Experience in this clinic is at variance with these observations, since, as subsequently mentioned, values for height and/or weight are significantly reduced in the majority of infants whose hemoglobin level is below 6 g/100 ml whole blood. Hypoproteinemia and mild edema of the face and eyelids are also seen in about one-third of these severely anemic infants.

Prevention and Treatment of Iron Deficiency

In preceding paragraphs, evidence was presented that iron-deficiency anemia and marginal deficiency states are far more prevalent than they should be in this country in an era when other nutritional deficiencies are rare. Some means of prophylaxis, therefore, deserves serious consideration. For reasons previously given, a prophylactic dose of iron cannot be rigidly defined. However, a recent study indicates that the administration of iron in the form of a concentrated ferrous sulfate preparation and in a dosage of 5 mg per day for infants three to six months of age and 10 mg daily thereafter effectively maintains the hemoglobin at 12 to 13 g/100 ml.[29]

If one objects to the routine administration of iron, some plan of prophylaxis should be adopted. The suggestions already made[8] are based on knowledge that iron depletion is particularly prevalent during pregnancy and in certain infants, and that iron-deficiency anemia cannot always be prevented by dietary means alone.

When prophylaxis has not been provided or has failed and anemia occurs, therapy with iron, as discussed in detail elsewhere[3,8,28,30] is necessary. The oral administration of a simple ferrous salt in adequate dosage constitutes the essential feature of such therapy. Complex mixtures containing a variety of minerals and vitamins are to be avoided because of the added expense of most and the potential toxicity of some. Parenteral iron preparations are not to be used indiscriminately. Whole blood transfusions are very seldom necessary. Should the characteristic therapeutic response fail to occur following the administration of 60–75 mg of elemental iron daily to an infant, or should anemia recur following an adequate response, one of several possible explanations, such as incorrect diagnosis, defective absorption, or blood loss, should be sought.

COPPER

For a period of about ten years following the work of Elvehjem and co-workers, referred to earlier, many conflicting reports appeared concerning the value of copper in the treatment of

iron-deficiency anemia. Although the positive evidence that copper acted as a useful adjunct in some infants was perhaps better than the negative[31] and although the concentration of copper in the liver of anemic infants was found to be much lower than in non-anemic ones[32], there was no proof that a deficiency of copper, analogous to that in experimental animals, occurred in the human infant as a result of a faulty diet. In very recent years, however, several reports of hypocupremia in infants have appeared, and have again stimulated interest in the possible occurrence of such a deficiency. The chief purposes of this section will be to review these newer findings and to summarize existing knowledge of the importance of copper in infant nutrition rather than to review in detail the metabolism of copper in man.

Copper Stores: It is known that the body of the newborn contains two to three times more copper per unit of body weight than the adult[6] and that this difference is largely due to a higher concentration of copper in the liver.

The physiologic significance of this congenital copper deposit is unknown, although often considered as being a wise provision of nature to tide the infant over a period when the diet contributes little copper. While teleologically sound, such a thesis cannot be staunchly supported until more is known of the absorption and availability of food copper, as well as of the requirements for copper in infancy. If this elevated concentration of copper in the liver of the newborn is in fact a wise provision of nature, then copper deficiency might be expected in the premature infant, since the total quantity of copper in his liver (0.4 to 3 mg) is characteristically lower by 50 per cent or more than that of the full-term infant.[33] Also the period during which the diet consists only of milk may be longer than in the full-term infant. Yet, Axtrup,[31] found no difference in the blood copper level between premature and term infants during the first six months of life.

The high concentration of copper in the liver of the newborn contrasts sharply with the generally low level in cord blood. The latter in turn contrasts with the uniformly elevated values in maternal blood during the last trimester of pregnancy.[4] Both the values for copper in maternal and cord blood fluctuate widely but apparently independently of one another (Table II). The significance of these changes is not known. Variations in cord blood copper probably do not reflect differences in the concentration of copper in fetal liver since characteristically the plasma copper level rises to the normal adult level of about 100 μcg per 100 ml in a few weeks.[4]

TABLE II

Lack of Correlation Between Copper Levels in Maternal and Cord Blood Plasma

Number of paired samples	Cord blood *mcg/100 ml*		Maternal blood *mcg/100 ml*	
	Range	Mean	Range	Mean
8	0–20	19	213–308	225
35	21–40	33	170–331	248
32	41–60	52	181–410	255
10	61–80	70	178–360	250
5	81–100	90	213–313	271
3	>100	121	250–305	270

Requirement: It has been estimated that the average adult can be maintained in positive copper balance on an intake of about 2 mg per day, i.e., approximately 0.03 mg/kg of body weight per day, and that children from 3 to 12 years of age need a somewhat greater amount, i.e., 0.05 to 0.1 mg/kg/day.[4] Even mediocre diets satisfy the requirements of both. While it might be assumed that the infant's requirements for copper are still higher, information is lacking on this point. The reverse may, in fact, be true, since neither anemia nor hypocupremia developed in two infants fed nothing but milk for four and five months, respectively. The same milk was effective in producing copper deficiency in swine.[34] Sweeping conclusions cannot be made, however, from these observations, since the growth rate of the subjects was distinctly subnormal, presumably as a result of multiple congenital anomalies.

Dietary Sources: Copper is widely distributed in foods, the content varying with the type of food and with the condition of the soil on which the plant or animal was raised. Foods particularly rich in copper, such as liver, kidney and brain, shell fish, nuts, etc., are usually

not included in the infant's diet. With the exception of such copper-rich foods, those foods which are of high-iron content are in general also of high-copper content and those low in iron are usually low in copper.[6]

From data on the copper content of various pureed and strained baby foods kindly supplied by the manufacturers and from sample diets as recommended in references on infant nutrition, an approximation of the amount of copper ingested by the "average" infant can be made (Table I). According to these data, a 6-month-old infant weighing about 8 kg would ingest 0.04 to 0.08 mg and a 12-month old infant of 10 kg would ingest about 0.08 mg copper per kg body weight per day. It has been estimated that about 5 per cent of the copper in an ordinary diet is retained.[6]

Milk has been recognized as a poor source of copper for years. The copper content of cow's milk is usually said to vary between 0.05 to 0.2 mg per liter, unless contaminated during processing, when values more than twice as high may be obtained.[6] Under current operating conditions, copper contamination of cow's milk is held to a minimum, through the use of glass and stainless steel equipment. This is done because the taste and keeping quality of milk are adversely affected if levels of about 1.5 mg copper per liter are permitted. Spectrographic analyses of six brands of homogenized milk recently obtained from local dairies yielded values for copper ranging from 0.015 to 0.14 mg per liter, with values below 0.037 mg per liter in four of the samples. Whether this finding is relevant to recent observations of hypocupremia in infants remains to be determined.

The copper content of human milk is somewhat higher than that of cow's milk, with values of 0.6 to 1.05 mg per liter existing during the first weeks of lactation but falling to 0.15 to 0.6 mg at the end of lactation. Apparently the addition of copper to a diet already containing adequate amounts of this metal has no effect on the copper content of milk.[6]

Copper Deficiency in Animals

Much has yet to be learned regarding the functions of copper in the human. It is obvious, however, from the variety of conditions developing in different species of animals as a result of a dietary deficiency of this element that its functions are multiple. Anemia always occurs but is variable in degree and type. Growth retardation, derangements of bone, diarrhea, demyelination of the spinal cord, depigmentation of hair, and myocardial fibrosis are additional examples of manifestations noted in different species under conditions of natural or artificial copper deprivation.[6] Furthermore, the clinical features of copper deficiency in a particular species of animal may be peculiar to that species. These facts are mentioned because of their effect on the interpretation of recent observations in the human subject.

In swine,[35] the anemia which develops as a result of copper deficiency is severe and closely resembles the anemia of iron deficiency (Table III). Thus, morphologically, the anemia is microcytic and hypochromic, and the bone marrow exhibits normoblastic hyperplasia. Even though liberal amounts of iron were given from the beginning of the experiment, biochemical alterations quite similar to those of iron-deficient animals develop. Thus, the serum iron level is reduced, the iron binding capacity of the serum is elevated, and the percentage saturation of the iron-binding protein is lowered. One notable chemical difference between the two groups is the profound hypo-

TABLE III

Summary of Hematologic and Chemical Values in Swine

Determination	Control	Copper-deficient	Iron-deficient
Hematocrit—ml/100 ml	42	22	21
Mean Cell Volume—cu μ	56	39	36
Mean Cell Hgb Concentration—%	33	29	28
Plasma Cu—μg/100 ml	186	15	207
Plasma Fe—μg/100 ml	175	38	30
Total Iron Binding Capacity—μg/100 ml	511	628	864
Saturation—%	34	6	3.5

cupremia in copper-deficient animals. This feature develops early and persists until copper is given, after which all manifestations of the deficiency are rapidly alleviated.

Several observations indicate that the metabolism of iron is seriously disturbed in copper-deficient swine.[35] Thus the ability to absorb iron from the intestinal tract and to mobilize iron from the tissues is impaired. Furthermore, the anemia is not relieved by the intravenous or intraperitoneal administration of large doses of iron. Additional data indicate, however, that the anemia is not simply due to defective absorption of iron but that there is also both a decrease in the survival time of erythrocytes and a limitation in the rate of synthesis of cells by the bone marrow.[34]

Copper Deficiency in Man

Several reasons have been given for doubting the existence of a dietary deficiency of copper in the human.[34] As far as the adult is concerned, this doubt is based on failure to find hypocupremia in patients subsisting on inadequate diets and on knowledge that the daily requirement for copper and the copper content of foods are such that death from caloric starvation would probably occur before a deficiency of copper resulted. Further evidence of the rarity of copper deficiency in the human comes from observations that the plasma copper level is almost always normal or elevated in infants with iron-deficiency anemia,[31,34] and from the previously cited observation that copper deficiency failed to develop in infants fed diets identical to those used in the experimental production of copper deficiency in swine.

Recently, however, hypocupremia has been noted in infants and children from various parts of the world.[37–41] A preliminary report of observations in this laboratory has been given.[42] In some of these patients, certain evidence suggests that a deficiency of copper exists. Thus, the severe microcytic hypochromic anemia and associated hypoferremia are quite analogous to the aforementioned observations in swine. Also a number of the infants have subsisted on almost nothing but milk for six months or longer. The previously mentioned practice of deliberately holding the copper content of milk to a minimum may then play an important etiologic role. On the other hand, because hypoproteinemia and edema have been conspicuous findings in many of the patients, an alternative suggestion has been offered, namely that the hypocupremia is conditioned by a transient reduction of the globulin, caeruloplasmin, which contains almost all of the copper in plasma. Some support for this thesis has been provided by studies in nephrosis[43] and in sprue.[34] Plasma copper and caeruloplasmin levels[44] are often reduced in nephrosis and are due, partially at least, to excessive urinary losses of protein-bound copper. And, although proof is lacking, it has been suggested that the hypocupremia noted in sprue is a result of defective absorption of copper. Excessive degradation of protein has been proposed as the cause of hypoproteinemia in the infants studied by Ulstrom *et al.*[41] Advocates for the belief that a conditioned rather than an actual deficiency of copper exists in the recently reported infants can also point out that the hypocupremia in newborns and in hepatolenticular degeneration (Wilson's disease) cannot be attributed to a dietary deficiency of copper and that hypoproteinemia has not been noted in copper-deficient animals.

On the basis of existing knowledge, it is impossible to state whether either, both, or neither of the above tentative explanations is the correct one. Nor is it known whether the hypocupremia is an expression of depletion of tissue copper or of diversion of copper to tissues during a period of "transient dysproteinemia." Indeed because the age groups, dietary histories, degree and characteristics of the anemia, etc. have not been identical in the material presented, a lack of homogeneity seems evident.

The majority of the infants with hypocupremia studied in this clinic have closely resembled those reported by Sturgeon and Brubaker.[40] Their ages have ranged from 6 to 17 months, the diets have consisted almost exclusively of homogenized milk. Severe anemia of the microcytic hypochromic type was present early, and varying degrees of generalized edema and growth failure were evident. The morphologic and chemical characteristics of the anemia in 12 affected infants are compared with the nor-

TABLE IV

Summary of Hematologic and Chemical Values in "Copper Deficiency" and Iron Deficiency in Infants

Determination	Normal	Copper deficiency	Iron deficiency
Number	27	12	37
Hemoglobin—g/100 ml	11.5	4.5	6.0
Hematocrit—ml/100 ml	37.7	16.2	22.7
Mean Cell Hgb Concentration—%	30.5	27.8	26.4
Plasma Cu—mcg/100 ml	169	60	172
Plasma Fe—mcg/100 ml	87	25	22
Total Iron Binding Capacity—mcg/100 ml	429	320	500
Saturation—%	20	7.8	4.3

mal and with infants having "uncomplicated" iron deficiency anemia (Table IV). A resemblance to similar data (Table III) obtained in copper-deficient swine is immediately apparent. Electrophoretic analyses of the serum proteins in the hypocupremic infants are compared in Table V with the values obtained in the same normal and iron-deficient subjects shown in the Table IV. To represent the serum proteins in iron-deficient infants as essentially normal is actually not true, but is done here for the sake of simplicity. We find hypoproteinemia and hypoalbuminemia in about 15 per cent of infants whose iron-deficiency anemia is unassociated with hypocupremia, and especially in those with less than 6.0 g hemoglobin per 100 ml blood. In addition to hypoalbuminemia, the infants with low plasma copper levels also exhibit a reduction in gamma globulin. The incidence of infection, however, was not notably higher in the hypocupremic infants. The production of antibodies in response to antigenic stimuli and the presence of normal numbers of plasma cells in the bone marrow of such infants has been reported.[41] The caeruloplasmin level was also reduced below the normal adult range of 27 to 38 mg/100 ml[44] in four of five hypocupremic infants so studied.* Caeruloplasmin levels ranged from 20.0 to 25.5 mg/100 ml in these patients and was 34.3 mg/100 ml in the other.

TABLE V

Summary of Serum Protein Values in "Copper Deficiency" and Iron Deficiency in Infants*

Determination	Normal	Copper-deficiency	Iron deficiency
Total Protein	6.89	4.5	6.5
Albumin	3.98	2.05	3.92
Alpha-1 globulin	0.378	0.459	0.358
Alpha-2 globulin	0.971	0.886	0.935
Beta globulin	0.836	0.795	0.841
Gamma globulin	0.726	0.347	0.618

* Results expressed in g/100 ml.

Complete recovery has occurred in infants given iron and copper even though continued on an exclusive milk diet, and has also occurred when the dietary intake has improved following iron therapy alone. Therapeutic results also indicate that neither the absorption of iron given orally nor the utilization of iron given intravenously is impaired, thus contrasting with observations previously made in copper-deficient swine. Also, by contrast with such animals, the administration of copper prior to iron therapy was not followed by significant changes in the serum iron, reticulocytes or hemoglobin in a single patient so studied. This finding suggests that body iron stores were markedly depleted. Several observations also suggest that depletion of tissue copper actually exists. Thus, the plasma copper level returned to normal rapidly following the oral administration of copper. A second reticulocyte peak was observed in one patient given copper after the maximum reticulocyte response to iron therapy had occurred. A low-copper content in the red blood cell was found in two of the four patients in whom this determination was made. It has been shown that erythrocyte copper does not decline in copper-deficient swine until the deficiency becomes severe. In addition, in two infants maintained on nothing but milk for six weeks, iron therapy was followed by a prompt restoration of hemoglobin, serum proteins and electrophoretic pattern to normal, but was not followed

* Performed through the courtesy of Dr. G. E. Cartwright, Salt Lake City, Utah.

by any significant change in the plasma copper level. During the seventh week, however, the level of plasma copper promptly rose from 50 to 240 μg/100 ml in the one patient given copper by mouth.

Correction of the protein abnormality in these two patients following iron administration also strongly suggests that the hypoproteinemia was secondary to iron rather than copper depletion. In this regard additional observations can be cited which indicate that other signs of malnutrition are not infrequent in infants with iron-deficiency anemia, especially when the latter is severe. In 25 infants whose hemoglobin level was below 6.0 g/100 ml of blood but whose plasma copper levels were not reduced, values for height and/or weight were below the tenth percentile in approximately 65 per cent. In about one-third of these patients, serum albumin levels were also subnormal. Thus, growth failure and hypoproteinemia are not exclusive features of the "hypocupremic syndrome" in infancy. Whether chronic anemia, chronic caloric undernutrition or a more subtle effect of iron depletion on nutrition account for these signs of malnutrition remains to be determined.

The above cited observations on infants exhibiting anemia, hypoferremia, hypoproteinemia are tentatively interpreted to indicate that both tissue copper and tissue iron depletion exist and that iron deficiency is a fundamental factor in the development of hypoproteinemia. Whether copper deficiency precedes and in some fashion precipitates or aggravates tissue protein depletion, whether the reverse is true, or whether copper and protein depletion occur simultaneously remain to be determined. As previously noted, copper deficiency in swine is not associated with alterations in serum proteins. On the other hand, hypocupremia has developed during the course of chronic protein depletion in swine,[45] but its mechanism has not been explored. In view of this finding, it seemed worthwhile to determine whether chronic protein depletion in children was also associated with hypocupremia. Through the cooperation of Dr. N. Scrimshaw, INCAP, Guatemala City, Guatemala, the sera of ten children ranging from 11 months to 11 years in age and suffering from kwashiorkor were analyzed. The average copper level was quite low, namely, 65 μg/100 ml, and values ranged from 43 to 86 μg/100 ml. Further studies on similar patients are planned.

In addition to these observations, two infants with chronic enteritis associated with edema and hypoproteinemia but unassociated with anemia or clinical evidence of gluten sensitivity have recently been studied. Both exhibited marked hypocupremia (26 and 12 μg/100 ml). The oral administration of copper, however, did not effect an immediate rise in the plasma copper level, and it was only after the diarrhea subsided and the nutritional state was repaired by appropriate therapy that a normal plasma copper level was attained. Even the parenteral administration of copper in a similar patient studied by Cartwright[46] failed to restore the plasma copper to normal. Although these findings might be explained on the basis of diversion of copper to tissues during the period of transient hypoproteinemia, it seems just as likely that protein and copper depletion existed simultaneously and that positive copper balance could not be attained until nitrogen equilibrium was restored. Copper-protein interrelationships may prove to be quite analogous to potassium-protein interactions, as recently demonstrated by Frazier and co-workers.[47]

It has been amply demonstrated that the metabolism of copper is altered during pregnancy and many pathologic states, as evidenced by an *increase* in the copper content of whole blood, erythrocytes and plasma.[4] It now appears that alterations in the metabolism of copper as evidenced by *hypocupremia* also occur in a variety of pathologic states, especially in infants and children and in disorders in which the metabolism of protein is disturbed. Further studies are obviously needed before the full significance and underlying causes of these changes will be known. Until such information is available it would seem unwise to recommend the therapeutic use of copper and premature to suggest that copper be added to certain foods or otherwise used in a prophylactic sense. However, since at least some affected infants appear to develop this syndrome

in association with iron deficiency, it can be recommended again that the physician be alert to the high incidence of iron depletion in infants and that he take a more active part in its prevention.

REFERENCES

1. ELVEHJEM, C. A.: The biological significance of copper and its relation to iron metabolism. *Physiol. Rev.* 15: 471, 1935.
2. DRABKIN, D. L.: Metabolism of the hemin chromoproteins. *Physiol. Rev.* 31: 345, 1951.
3. JOSEPHS, H. W.: Iron metabolism and the hypochromic anemia of infancy. *Medicine* 32: 125, 1953.
4. CARTWRIGHT, G. E.: Copper metabolism in human subjects, in *Copper Metabolism: A Symposium on Animal, Plant and Soil Relationships*, ed. by W. D. McElroy and B. Glass, Johns Hopkins Press, Baltimore, 1950, p. 274.
5. GUPLER, C. J.: Copper metabolism in man. *J.A.M.A.* 161: 530, 1956.
6. UNDERWOOD, E. J.: *Trace Elements in Human and Animal Nutrition*. Academic Press, Inc., New York, 1956.
7. GUEST, G. M., and BROWN, E. W.: Erythrocytes and hemoglobin of the blood in infancy and childhood. III. Factors in variability, statistical studies. *A.M.A. J. Dis. Child.* 93: 486, 1957.
8. LAHEY, M. E.: Iron deficiency anemia. *Pediat. Clin. North America* 4: 481, 1957.
9. STURGEON, P.: Studies of iron requirements in infants and children. I. Normal values for serum iron, copper and free erythrocyte protoporphyrin. *Pediatrics* 13: 107, 1954.
10. HEATH, C. W., and PATEK, A. J., Jr.: Anemia of iron deficiency. *Medicine* 16: 267, 1937.
11. STURGEON, P.: Iron metabolism: A review with special consideration of iron requirements during normal infancy. *Pediatrics* 18: 267, 1956.
12. JOSEPHS, H. W.: Hypochromic microcytic anemia of infancy: Iron depletion as a factor. *Pediatrics* 18: 959, 1956.
13. WIDDOWSON, E. M., and SPRAY, C. H.: Chemical development in utero. *Arch. Dis. Childhood* 26: 205, 1951.
14. WILSON, E. E., WINDLE, W. F., and ALT, H. L.: Deprivation of placental blood as cause of iron deficiency in infants. *Am. J. Dis. Child.* 62: 320, 1941.
15. CHOWN, B.: Anaemia from bleeding of the fetus into the mother's circulation. *Lancet* 1: 1213, 1954.
16. WICKSTER, G. Z., and CHRISTIAN, J. R.: Post-hemorrhagic shock in the newborn infant. *Pediat. Clin. North America* 1: 555, 1954.
17. STRAUSS, M. B.: Anemia of infancy from maternal iron deficiency in pregnancy. *J. Clin. Investigation* 12: 345, 1933.
18. GUEST, G. M.: Hypoferric anemia in infancy. Robert Gould Research Foundation, Cincinnati 1: 144, 1947
19. HOLLY, R. G.: Intravenous iron: Evaluation of the use of saccharated iron oxide in iron deficiency states in obstetrics and gynecology. *Blood* 6: 1159, 1951.
20. WOODRUFF, C. W., and BRIDGEFORTH, E. B.: Relationship between the hemogram of the infant and that of the mother during pregnancy. *Pediatrics* 12: 681, 1953.
21. SMITH, N. J., ROSELLO, S., SAY, M. B., and YEYA, K.: Iron storage in the first five years of life. *Pediatrics* 16: 166, 1955.
22. STEARNS, G., and STINGER, D.: Iron retention in infancy. *J. Nutrition* 13: 127, 1937.
23. SMITH, C. A., CHERRY, R. B., MALETSKOS, C. J., GIBSON, J. G., 2nd, ROBY, C. C., CATON, W. L., and REID, D. E.: Persistence and utilization of maternal iron for blood formation during infancy. *J. Clin. Investigation* 34: 1391, 1955.
24. GUBLER, C. J.: Absorption and metabolism of iron. *Science* 123: 87, 1956.
25. BROKAW, K. F., SEDAM, M. S., and CASSIRER, A. M.: Influence of diet on the physiologic anemia of infants. *J. Pediat.* 21: 769, 1942.
26. MOORE, C. V.: Importance of nutritional factors in the pathogenesis of iron-deficiency anemias. AM. J. CLIN. NUTRITION 3: 3, 1955.
27. STEARNS, G., and MCKINLEY, J. B.: Conservation of blood iron during the period of physiological hemoglobin destruction in early infancy. *J. Nutrition* 13: 143, 1937.
28. WINTROBE, M. M.: *Clinical Hematology*, ed. 4, Lea & Febiger, Philadelphia, 1956.
29. NICCUM, W. L., JACKSON, R. L., and STEARNS, G.: Use of ferric and ferrous iron in the prevention of hypochromic anemia in infants. *A.M.A. Am. J. Dis. Child.* 86: 553, 1953.
30. COLEMAN, D. H., STEVENS, A. R., JR., and FINCH, C. A.: Treatment of iron deficiency anemia. *Blood* 10: 567, 1955.
31. AXTRUP, S.: *The Blood Copper in Anemias of Children with Special Reference to Premature Cases*, Lund, Sweden, P. H. Lindstedt Universitats Bokhandel, 1946.
32. CHOU, T. P., and ADOLPH, W. H.: Copper metabolism in man. *Biochem. J.* 29: 476, 1935.
33. RAMAGE, H., SHELDON, J. H., and SHELDON, W.: Spectrographic investigation of metallic content of the liver in childhood. *Proc. Roy. Soc. London, S. B.* 113: 308, 1933.
34. CARTWRIGHT, G. E.: The relationship of copper, cobalt, and other trace elements to hemopoiesis. AM. J. CLIN. NUTRITION 3: 11, 1955.
35. LAHEY, M. E., GUBLER, C. J., CHASE, M. S., CARTWRIGHT, G. E., and WINTROBE, M. M.: Studies on copper metabolism. II. Hematologic manifestations of copper deficiency in swine. *Blood* 7: 1053, 1952.

36. GUBLER, C. J., LAHEY, M. E., CHASE, M. S., CARTWRIGHT, G. E., and WINTROBE, M. M.: Studies on copper metabolism. III. The metabolism of iron in copper deficient swine. *Blood* 7: 1075, 1952.

37. PANIZON, F., and CANTARUTTI, F.: La cupremia nei distrofici. *Lattante* 26: 24, 1955.

38. STRANSKY, E., DAUIS-LAWAS, D. T., and LAWAS, I. L.: On serum copper level and its importance in childhood. *Ann. Paediat.* 179: 1, 1952.

39. ZURUKZOGLU-SKLAVOUNOU, S.: Hypochrome Anämie im Kindesalter. *Helvetica Paediatrica Acta* 8: 251, 1953.

40. STURGEON, P., and BRUBAKER, C.: Copper deficiency in infants. A syndrome characterized by hypocupremia, iron deficiency anemia, and hypoproteinemia. *A.M.A. Am. J. Dis. Child.* 92: 254, 1956.

41. ULSTROM, R. A., SMITH, N. J., and HEIMLICH, E. M.: Transient dysproteinemia in infants, a new syndrome. 1. Clinical studies. *A.M.A. Am. J. Dis. Child.* 92: 219, 1956.

42. LAHEY, M. E., and SCHUBERT, W. K.: New deficiency syndrome occurring in infancy. *A.M.A. Am. J. Dis. Child.* 93: 31, 1957.

43. CARTWRIGHT, G. E., GUBLER, C. J., and WINTROBE, M. M.: Studies on copper metabolism. XI. Copper and iron metabolism in the nephrotic syndrome. *J. Clin. Investigation* 33: 685, 1954.

44. MARKOWITZ, H., GUBLER, C. J., MAHONEY, J. P., CARTWRIGHT, G. E., and WINTROBE, M. M.: Studies on copper metabolism. XIV. Copper, ceruloplasmin and oxidase activity in sera of normal human subjects, pregnant women, and patients with infection, hepatolenticular degeneration and the nephrotic syndrome. *J. Clin. Investigation* 34: 1498, 1955.

45. CARTWRIGHT, G. E., and WINTROBE, M. M.: Studies on free erythrocyte protoporphyrin, plasma copper, and plasma iron in protein deficient and iron-deficient swine. *J. Biol. Chem.* 176: 571, 1948.

46. Personal communication.

47. FRAZIER, L. E., HUGHES, R. H., and CANNON, P. R.: The relationship between potassium utilization and nitrogen balance. AM. J. CLIN. NUTRITION 4: 655, 1956.

Clinical and Biochemical Observations in Galactosemia

By KURT J. ISSELBACHER, M.D.*

IT IS now well known that the disease, galactosemia, represents an inborn and hereditary error in the metabolism of galactose. More than 40 cases have been reported in the literature up to the present time† and many more unreported cases have been discovered in the course of investigations on this disease. Thus, although the condition is a rare one, it probably occurs not as infrequently as was heretofore believed.

It is the purpose of this communication to review the clinical aspects of galactosemia, to discuss in detail the recently elucidated biochemical defect considered to be the basic disturbance of this condition, to emphasize newer methods of diagnosis, and, finally, to comment on the factors possibly contributing to the toxic manifestations of the disease.

CLINICAL FEATURES

The symptoms which occur in galactosemia usually manifest themselves shortly after birth and are known to be causally related to the ingestion of milk or galactose. The main features include early nutritional failure, mental retardation, hepato-splenomegaly, osteoporosis and cataracts. Afflicted infants usually appear normal at birth, but after a few days of milk ingestion they readily develop vomiting and diarrhea together with lethargy and drowsiness. Jaundice is a very common finding as the disease progresses and is usually associated with enlargement of the liver and spleen. The hepatomegaly is initially due to fatty infiltration, but in the later stages cirrhosis ensues. In severe cases the disease is often fulminating and death may occur in the neonatal period or soon thereafter. If the clinical condition extends beyond a period of four to eight weeks, one can usually detect evidence of mental retardation and cataract formation. Both symptoms tend to become increasingly prominent as galactose ingestion continues. A frequent occurrence is the development of hypoglycemia when blood galactose levels are significantly elevated. This syndrome may readily escape detection if only total blood sugar determinations are performed.

The earliest clue to the diagnosis comes with the finding of a reducing sugar (galactose) in the urine. This sugar, unlike glucose, is not fermented by yeast and also is not a substrate for the enzyme glucose oxidase. The recently introduced clinical test papers (e.g. Clinistix®, Tes-Tape®) which utilize the glucose oxidase reaction will thus be negative. It is important to emphasize that the galactosuria is inconstant and can be absent on the routine admission urinalysis of a patient who, because of persistent vomiting, may not have been able to absorb much of the ingested milk. In contrast to the galactosuria, the tolerance of orally or intravenously administered galactose is always significantly impaired. For this reason the performance of the galactose tolerance test has often been considered necessary for the diagnosis of the disease. This test is not without hazard, however, because of the frequent occurrence of hypoglycemia as well as the pos-

From the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., the Department of Medicine, Harvard Medical School, and the Medical Service, Massachusetts General Hospital, Boston, Mass.

* Instructor in Medicine, Harvard Medical School, and Assistant in Medicine, Massachusetts General Hospital, Boston, Mass.

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† Extensive bibliographies citing individual case reports may be found by consulting references 1 to 3.

sible deleterious effects of the additional galactose. More recently a newer and more specific enzymatic test has been described (*vide infra*) which obviates the need for the galactose tolerance test.

The other usual urine abnormalities consist of albuminuria and amino-aciduria.[6] The amino-acid pattern has been essentially similar in all cases, with a predominance of the neutral, simple aliphatic chain type; i.e. serine, glycine, alanine, threonine, glutamine, and valine; in addition phenylanine, lysine, cystine, glutamic acid, methyl histidine, tyrosine and amino-isobutyric acids have been detected in the urines of these patients.[4,5]

NUTRITIONAL THERAPY

Fortunately, one of the striking features of this disease is the remarkable improvement which occurs when these patients are placed on galactose-free diets. If the disease is not too advanced, all of the symptoms may regress and even disappear completely with dietary restrictions only. One readily observes rapid weight gain and cessation of nausea, vomiting and diarrhea. The liver and spleen return to normal size. Cirrhosis, if present, has been known to disappear completely.[1] The urinary abnormalities mentioned above likewise promptly cease. Cataracts, if present, often regress somewhat and in some instances they may disappear completely.[2] The major symptom which usually shows no improvement is the mental retardation. It has been observed by most authors that the central nervous system damage may not improve despite the most rigid adherence to a galactose-free diet. It is for this reason that early diagnosis and prompt institution of therapy are so important.

Galactose-free diets can readily be instituted in infancy by resorting to any of a number of commercially available milk substitutes such as Nutramigen®, Dextri-Maltose® or soy bean preparation. It has been amply demonstrated that these diets are compatible with normal growth and development. Although Platt[7] feels that galactose ingestion may be of special benefit and that galactose is poorly synthesized in the body, there is at present no definite clinical evidence that central nervous system function, or somatic development in general, is impaired by the prolonged use of galactose-free diets. There is ample evidence, as indicated herein, that patients with galactosemia possess the enzyme, UDP Galactose-4-epimerase, which would allow for endogenous synthesis of galactose from glucose and hence permit galactolipid formation in the central nervous system[8] and elsewhere.

It has been frequently observed that patients with galactosemia may in later years of life ingest varying quantities of galactose without experiencing any significant side effects.[1] This is probably related to two factors: (a) the improvement in the tolerance to galactose in these patients with increasing age; and (b) the fact that in later years the ratio of ingested galactose to body weight or surface area is far smaller than in the neonatal period when the symptoms are so pronounced.

BIOCHEMICAL STUDIES

(*A*) *Normal Galactose Metabolism*

Considerable knowledge has been gained in recent years concerning the metabolism of galactose and its utilization in the body. Most of the ingested dietary galactose is in the form of lactose, the main carbohydrate of milk, which in the intestine is split into its two component monosaccharides, galactose and glucose (Fig. 1). These sugars differ only in the orientation

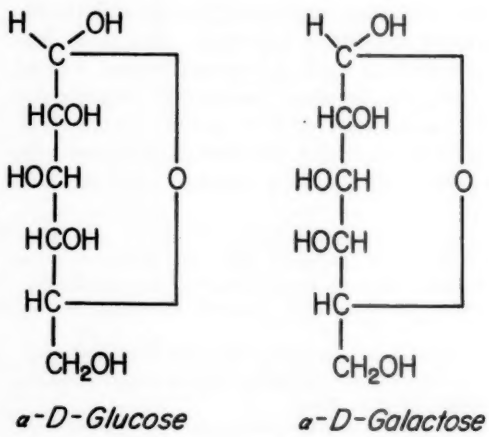

Fig. 1. Comparison of the structure of α-D-glucose and α-D-galactose.

of the hydrogen and hydroxyl groups about the fourth carbon atom. The galactose may be incorporated into galactolipids, and muco-polysaccharides (chondroitin sulfate) but most of it is converted to glucose derivatives which can then be utilized for energy. The exact manner whereby galactose enters the glucose "energy pool" has been greatly elucidated as a result of the investigations of Leloir, Kalckar and their associates.[8–11]

The first step in this direction consists in the phosphorylation of galactose α-galactose-1-phosphate (Reaction I). This requires adenosine triphosphate (ATP) and a specific enzyme, galactokinase.

(I) Galactose + ATP → Galactose-1-P + ADP

The galactose-1-phosphate is then converted to glucose-1-phosphate by a second reaction (II) which involves a specific nucleotide, uridine diphosphoglucose (UDPGlucose). In this reaction the galactose-1-phosphate is transferred to the nucleotide to yield uridine diphospho-galactose (UDPGalactose) while at the same time glucose-1-phosphate is liberated. The enzyme catalyzing this reaction has been called phospho-galactose uridyl transferase or, more simply, P-Gal transferase.

(II) Galactose-1-phosphate + UDPGlucose ⇄ UDPGalactose + Glucose-1-phosphate

In a third reaction (III) the two uridine nucleotides are interconverted in a manner which is still incompletely understood at the present time. It has recently been observed that diphosphopyridine nucleotide (DPN) is a cofactor for the reaction and it is believed that a 4-keto sugar may be an intermediate.[12] The enzyme has previously been called galactowaldenase but in view of the recent observations on the probable mechanism of the reaction it is perhaps better called UDPGalactose-4-epimerase.[8]

(III) UDPGalactose $\overset{\text{DPN}}{\rightleftarrows}$ UDPGlucose

(B) *The Enzymatic Defect in Galactosemia*

In studies on the possible causes of galactosemia it seemed reasonable to presume that the defect might involve one or more of the above reactions. A clue in this direction came from the observations of Schwarz *et al.*,[13] who demonstrated that galactose-1-phosphate accumulated in the red blood cells of galactosemic subjects upon the ingestion of milk or of galactose. We were able to confirm these observations with *in vitro* experiments in which it was shown the galactosemic erythrocytes when incubated in a medium containing galactose showed a significant accumulation of galactose-1-phosphate, in contrast to normal red cell similarly incubated.[14] This suggested that the defect in galactosemia could be due to a block in the conversion of galactose-1-phosphate to glucose-1-phosphate, and that such a block might reasonably involve the enzyme P-Gal transferase.

In further studies it was observed that the normal red cell is able to catalyze all three reactions referred to above.[15] In contrast, erythrocytes from galactosemic patients, while normal with respect to their content of enzymes I and III, showed a striking absence of P-Gal transferase activity. This observation has been confirmed in over 20 cases of galactosemia studied thus far. These galactosemic red cells did not lack any co-factors nor did they contain demonstrable inhibitors to account for the lack of transferase activity. It was initially reasoned that the absence of the enzyme might simply be due to an adaptive phenomenon; that is, since many of the galactosemic patients tested had been off galactose for extended periods of time, the red cells might gradually have lost their transferase activity. However, when erythrocytes of patients who had been off galactose for as long as 18 months were examined they were found to be normal with respect to all three enzymes. Also, more recently, it was shown in one patient that the transferase deficiency existed at birth by demonstrating the absence of the transferase in the cord blood of an infant afflicted with the disease.[16] The enzymatic defect noted in the red cells has also been investigated in the liver, which normally contains significant amounts of the enzymes. In two galactosemic patients analysis of liver tissue obtained by biopsy revealed only traces of transferase activity compared to normal liver obtained at biopsy.[16]

(C) *Possible Alternate Routes of Galactose Metabolism*

Observations have been made by several groups of investigators to suggest that administered galactose can be metabolized to some degree in galactosemic patients.[3] These conclusions have been based on the fact that anywhere from 30 to 80 per cent of the ingested galactose is retained and not accounted for by urinary excretion of the sugar. From the observations of Schwarz *et al.*[13] one would expect of course that some of this retained galactose would be in the form of galactose-1-phosphate. Recent studies performed with C^{14}-labeled galactose in a 24-year-old male with galactosemia have permitted a more definite investigation of this problem.[17] Although this patient's ability to metabolize galactose was only one per cent compared to the normal, it was shown that 3 per cent of the administered galactose could be accounted for in his urine as a glucosiduronic acid. In view of our knowledge of the mechanism of glucosiduronic acid formation, this suggests very strongly that at least 3 per cent of the galactose must have been converted to a glucose metabolite (via the urine nucleotides). These studies would indicate that either the observed enzymatic defect in galactosemia is incomplete or that there exists a possible alternate or accessory pathway for galactose metabolism. Any such pathway probably could not be a major route for galactose metabolism, for otherwise one would never see the pronounced clinical manifestations in this disease subsequent to galactose ingestion.*

(D) *New Spectrophotometric Test for Galactosemia*

It has been customary to confirm the diagnosis of galactosemia by means of the oral or intravenous galactose tolerance test. As mentioned above, this test is not without hazard in an infant in whom there is a marked impairment of galactose metabolism. As a result of the discovery of the enzymatic defect in galactosemia a relatively simple spectrophotometric test has been developed which can readily be performed on blood specimens. This test, the details of which have been described elsewhere,[18] is both specific and sensitive. Thus far no false positives have been detected. Errors may occur, however, if the patient has been transfused with normal blood within three months prior to the assay. In such a situation, the transferase content of the donor cells may give a false negative result.[16]

In a newborn suspected of having galactosemia, the enzymatic method permits a diagnosis to be made (on cord blood) without exposing the infant to the possible hazards of galactose administration in order to arrive at the diagnosis. Traces of activity might be ascribed to admixtures of maternal blood and warrants therefore a second test one month later. The enzymatic method may in addition prove more useful than the galactose tolerance test in elucidating the hereditary aspects of galactosemia.

(E) *Genetic Factors*

It is quite evident that galactosemia is a hereditary disease but the exact genetic pattern has not been established. Although the disease occurs frequently in siblings, their parents never show any clinical manifestations. By means of the galactose tolerance test Holzel and Komrower[19] demonstrated that in the majority of cases usually one of the parents showed a lowering of the galactose tolerance test. It is conceivable that with a refinement of the transferase assay one may be able to pick up traits of this disease more readily. However, Dr. Richard Post of the Institute for Human Variation (Columbia University) has suggested[20] that the inheritance of the disease might be based on two multiple alleles, in which case one would have to look for still another deranged metabolic pattern that has thus far escaped our attention as a trait.

(F) *Possible Factors in the Toxicity of Galactosemia*

Recent animal studies have shed considerable light on factors possibly contributing to the pronounced physiologic disturbances which occur in galactosemia. It has been observed repeatedly that when animals (rats or chicks)

* Since the submission of this manuscript, evidence for such an accessory pathway of galactose metabolism has been obtained in this laboratory (Isselbacher, K. J.: *Science* (in press)).

are placed on 30 per cent galactose diets they frequently show a typical quivering syndrome and uniformly develop cataracts within a period of 14 to 21 days.[21,23] Examination of the lenticular[23] and hepatic tissues[24] of such animals has demonstrated the accumulation of galactose-1-phosphate, just as is the case in the galactosemic red cells. It is tempting to speculate that this hexose-phosphate accumulation might interfere with or inhibit one or more enzyme systems which in turn could lead to the physiologic disturbances seen experimentally and clinically. In line with this reasoning Schwarz *et al.*[13] have shown that the accumulation of galactose-1-phosphate in the red cells is associated with a reduced oxygen consumption of these cells.

Hansen *et al.* have studied the uridine nucleotide patterns in the livers of galactose-fed chicks.[21] They found the UDPglucose levels greatly reduced and the UDPgalactose content increased. In similar studies on galactose-fed rats and using specific enzymatic methods we have not been able to find any reduction in the hepatic concentration of UPD-glucose.[22]

The hypoglycemia which often occurs in galactosemia has also been considered by many as being causally related to the clinical manifestations of this disease. However it should be recalled that most of the symptoms found in galactosemia do not occur in diseases associated with more pronounced hypoglycemia, as in von Gierke's disease.

SUMMARY AND CONCLUSIONS

Galactosemia constitutes a hereditary disease in which galactose cannot be metabolized normally. The outstanding features are nutritional failure, hepato-splenomegaly with cirrhosis, mental retardation and cataract formation. Laboratory studies reveal a decreased galactose tolerance, galactosuria, albuminuria and amino-aciduria.

Effective treatment is possible by the institution of a galactose-free diet. Complete disappearance of symptoms may occur if the diagnosis is made early and the dietary regimen is promptly instituted.

The disease results from the congenital deficiency of a specific enzyme, P-Gal transferase (phospho-galactose uridyl transferase). As a consequence, galactose cannot be properly utilized and galactose-1-phosphate accumulates in the tissues. The latter accumulation may be causally related to the toxic manifestations observed clinically.

In spite of the known enzymatic defect some galactose utilization has been shown to occur in these patients. Reference is made to the use of a new and specific enzymatic blood assay for the diagnosis of galactosemia. The advantages of this procedure over the galactose tolerance test are presented.

REFERENCES

1. Townsend, E. H., Mason, H. H., and Strong, P. S.: Galactosemia and its relation to Laennec's cirrhosis: review of literature and presentation of six additional cases. *Pediatrics* 7: 760, 1951.
2. Ritter, J. A., and Cannon, E. J.: Galactosemia with cataracts: report of a case with notes on physiopathology. *New England J. Med.* 252: 747, 1955.
3. Komrower, G. M., Schwarz, V., Holzel, A., and Golberg, L.: A clinical and biochemical study of galactosemia. *Arch. Dis. Childhood* 31: 254, 1956.
4. Holzel, A., Komrower, G. M., and Wolson, V. K.: Amino-aciduria in galactosemia. *Brit. Med. J.* 1: 194, 1952.
5. Hsia, D. Y., Hsia, H., Green, S., Kay, M., and Gellis, S. S.: Amino-aciduria in galactosemia. *A. M. A. J. Dis. Child.* 88: 458, 1954.
6. Cusworth, D. C., Dent, C. E., and Flynn, F. V.: Amino-aciduria in galactosemia. *Arch. Dis. Childhood* 30: 150, 1955.
7. Platt, B. S.: Human nutrition and the sophistication of foods and feeding habits. *Brit. Med. J.* 1: 179, 1955.
8. Kalckar, H. M.: Biochemical mutations in man and microorganisms. *Science* 125: 105, 1957.
9. Leloir, L. F.: The metabolism of hexosephosphates in *Phosphorus Metabolism*, Vol. I (ed. by W. D. McElroy and B. Glass), Johns Hopkins Press, Baltimore, 1951, p. 67.
10. Leloir, L. E.: Enzymatic transformation of uridine diphosphate glucose into galactose derivative. *Arch. Biochem.* 33: 186, 1951.
11. Kalckar, H. M., Braganca, B., and Much-Petersen, A.: Uridyl transferases and the formation of uridine diphosphate galactose. *Nature* 172: 1038, 1953.
12. Maxwell, E. S.: Diphosphopyridine nucleotide, a cofactor for galactowaldenase. *J. Am. Chem. Soc.* 78: 1074, 1956.

13. SCHWARZ, V., GOLBERG, L., KOMROWER, G. M., AND HOLZEL, A.: Some disturbances of erythrocyte metabolism in galactosemia. *Biochem. J.* 62: 34, 1956.
14. KALCKAR, H. M., ANDERSON, E. P., AND ISSELBACHER, K. J.: Galactosemia, a congenital defect in a nucleotide transferase. *Biochim. et Biophys. Acta* 20: 262, 1956.
15. ISSELBACHER, K. J., ANDERSON, E. P., KURAHASHI, K., AND KALCKAR, H. M.: Congenital galactosemia, a single enzymatic block in galactose metabolism. *Science* 123: 635, 1956.
16. ANDERSON, E. P., KALCKAR, H. M., AND ISSELBACHER, K. J.: Defect in the uptake of galactose-1-phosphate into liver nucleotides in congenital galactosemia. *Science* 125: 113, 1957.
17. EISENBERG, F., JR., ISSELBACHER, K. J., AND KALCKAR, H. M.: Studies in the metabolism of carbon-14-labelled galactose in a galactosemic individual. *Science* 125: 116, 1957.
18. ANDERSON, E. P., KALCKAR, H. M., KURAHASHI, K., AND ISSELBACHER, K. J.: A specific enzymatic assay for the diagnosis of congenital galactosemia. *J. Lab. & Clin. Med.* (In press).
19. HOLZEL, A., AND KOMROWER, G. M.: A study of the genetics of galactosemia. *Arch. Dis. Childhood* 30: 155, 1955.
20. KALCKAR, H. M.: Biochemical mutations in man and microorganisms. *Science* 125: 107, 1957.
21. HANSEN, R. G., FREEDLAND, R. A., AND SCOTT, H. M.: Lactose metabolism, V. The uridine nucleotides in galactose toxicity. *J. Biol. Chem.* 219: 391, 1956.
22. ISSELBACHER, K. J.: Unpublished observations.
23. SCHWARZ, V., AND GOLBERG, L.: Galactose-1-phosphate in galactose cataract. *Biochim. et Biophys. Acta* 18: 310, 1955.
24. KOSTERLITZ, H. W.: Structure of galactose-phosphate present in liver during galactose assimilation. *Biochem. J.* 37: 318, 1943.

The Pathogenesis of Idiopathic Hypercalcemia in Infancy

By THOMAS STAPLETON, D.M., M.R.C.P.,* WILLIAM B. MACDONALD, M.D., M.R.C.A.P.,† AND REGINALD LIGHTWOOD, M.D., F.R.C.P.‡
With the Technical Assistance of I. W. J. Evans

THE PURPOSE of this article is to review the chemical changes which have been found in cases of idiopathic hypercalcemia, and to discuss the etiology and treatment of the disease. The clinical features have been described elsewhere.[1] In summary, all cases have commenced in the first year of life, sometimes as early as a few weeks after birth, but usually at about five months, with anorexia, vomiting, constipation and failure to gain weight normally. Some cases have one or more of the following features: thirst, polyuria, occasional spikes of fever, a systolic murmur, hypertension, osteosclerosis, a peculiar facies and mental retardation.[2] In general it can be said that the earlier the onset and the more severe the symptoms, the more likely are complicating features to be present.

CHEMICAL DESCRIPTION

The characteristic chemical changes are a rise in the level of serum calcium and blood urea. Other changes may occur as well: hypercholesterolemia, rise in α_2 globulin, acidosis, and a low serum alkaline phosphatase.

Calcium

Because of the possibility of an inaccurate laboratory estimation and because a transient rise in the serum calcium level can occur in other diseases, we have only considered the diagnosis of idiopathic hypercalcemia when two estimations of the serum calcium have been at least 12 mg/100 ml. The highest recorded value is 23 mg/100 ml by Cordeiro,[3] but in the United Kingdom the highest is 19 mg/100 ml.[4] The distribution of the increase of serum calcium between the protein-bound and soluble fractions has not been determined. There is no constant relationship between the degree of hypercalcemia and plasma protein levels. The daily excretion of calcium in the urine is raised. Amounts as large as 148 mg in 24 hours have been found.[5] Other reports[4,6,7,8] all give figures well above the normal daily excretion which is of the order of 20 to 30 mg.[8]

In spite of the increased urinary calcium excretion, the calcium balance is strongly positive (Fig. 1). In reported balance studies the calcium retention expressed as a percentage of calcium intake has varied between 31 and 69 per cent in eleven cases, with an average of 49 per cent.[4,5,6,8]

Phosphorus

The serum phosphorus is usually in the normal range of 3.5 to 5.5 mg/100 ml sometimes slightly higher, sometimes lower. In the early stages of the illness, when the impairment of renal function is minimal, there appears to be no constant relationship to the serum calcium level. In the more advanced stage of the illness the serum phosphorus may be abnormally high.

When the serum calcium is high, the phosphorus balance is strongly positive (Fig. 1). In seven reported balance studies,[4,5,8] the phosphorus retention expressed as a percentage

From the Pediatric Unit, St. Mary's Hospital Medical School, London.

* Assistant Director, Pediatric Unit, St. Mary's Hospital Medical School, London.

† Lecturer, Pediatric Unit, St. Mary's Hospital Medical School, London.

‡ Director, St. Mary's Hospital Medical School, London.

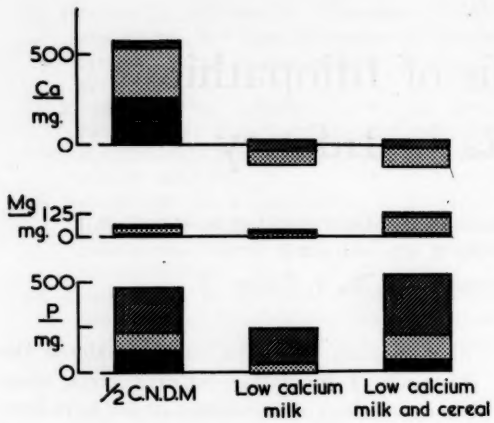

Fig. 1. Treatment related to daily calcium, magnesium and phosphorus balances, which are averages of four-day collections. (Urinary excretion hatched, stool excreted dotted, positive balance black). (From: *Lancet* 1: 932, 1956.)

of phosphorus intake has varied between 26 and 84 per cent with an average of 51 per cent.

Magnesium

We have estimated the serum magnesium in seven children. Values ranged from 1.8 to 2.7 mg/100 ml, confirming the findings of other workers.[6] In only one case did there appear to be any relation with the rise and fall of serum calcium (Fig. 2) and in that patient the magnesium also paralleled the changes in serum phosphate and urea. It therefore seems likely that the changes were due to fluctuations in renal function. The magnesium balance seems to be unaffected throughout the course of the illness[5,9] (Fig. 2).

Bicarbonate

In most cases of idiopathic hypercalcemia the serum bicarbonate is within normal limits. Some infants may have an abnormally low serum bicarbonate even when renal function is not greatly impaired.[10] It is possible that some infants with hypercalcemia have an associated renal acidosis.[11] There appears to be no direct relationship between serum calcium and bicarbonate.

Sodium, Potassium Chloride

The serum concentration of these electrolytes are within normal limits in idiopathic hypercalcemia of infancy. There is no disturbance of the sodium, chloride or potassium balances.[9]

Proteins

In his original description of the biochemical changes in idiopathic hypercalcemia, Payne[12] stated that the plasma proteins showed an in-

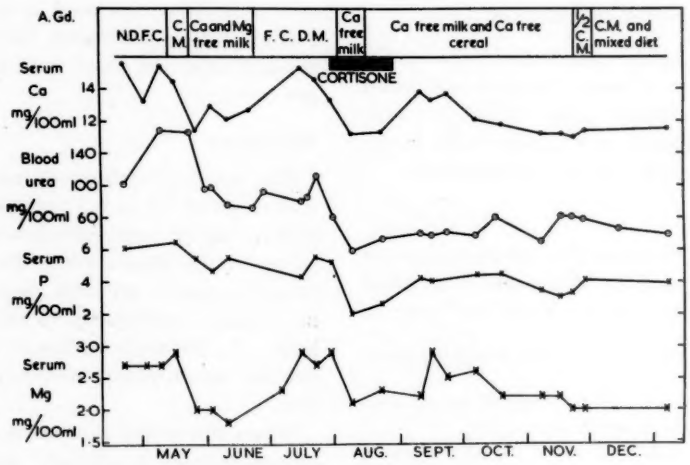

Fig. 2. Treatment related to blood urea, and serum calcium, phosphorus and magnesium. (Modified from *Acta Paediat.* 44: 559, 1955.)

crease in the α_2- and γ-globulin fractions. These findings have been confirmed by other investigators, but only in some cases of idiopathic hypercalcemia.[6,13] Only two out of seven infants studied by us have had total serum proteins higher than 7 g/100 ml, but in all of the seven the α_2-globulin fraction was significantly raised, although the γ-globulin was normal. The α_1- and β-fractions are occasionally slightly raised.

Cholesterol

In severe cases serum cholesterol levels may be of the order of 300 to 400 mg/100 ml. In infants with an illness of intermediate severity, the serum cholesterol is often increased to 250 to 300 mg/100 ml, and returns to normal levels when the serum calcium falls and clinical improvement commences.

TABLE I

Serum Calcium Levels Related to Serum Citrate Levels and Diet

Patient	Diet	Serum calcium *mg/100 ml*	Serum citrate *mg/100 ml*
C. Hm.	Vitamin D fortified dried milk	13.4	3.0
	Low-calcium diet	12.0	1.5
	Low-calcium diet with added solids	12.1	3.6
	Low-calcium diet with added solids	11.2	1.8
S. Fk.	Vitamin D fortified dried milk	13.1	2.7
	Low-calcium diet	11.1	2.2
J. Gh.	Vitamin D fortified dried milk	13.2	2.6
	Vitamin D fortified dried milk	12.1	2.0
	Low-calcium milk	11.1	1.9
	Low-calcium milk	11.0	1.3
	Equal parts whole milk and low-calcium milk	11.7	2.7
A. Pr.	Vitamin D fortified dried milk	15.1	3.1
	Vitamin D fortified dried milk	13.7	2.8
	Low-calcium diet	11.8	3.5
	Low-calcium diet	12.7	2.1
	Low-calcium diet	12.2	2.0
	Low-calcium diet	11.5	1.7
	Low-calcium diet with added solids	11.2	4.0
	Low-calcium diet with added solids	10.9	3.6

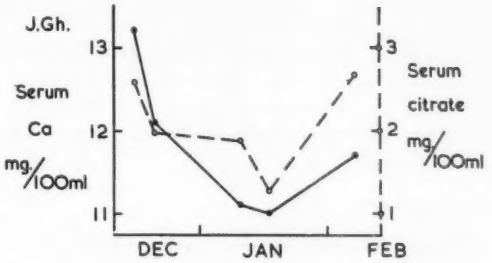

Fig. 3. The variable relationship between the serum citrate and serum calcium levels.

Alkaline Phosphatase

Low concentrations of this enzyme are often found in the active phase of the disorder, particularly in severely affected cases when osteosclerosis is a complicating feature. Levels of 4 to 8 King-Armstrong units are not uncommon. The concentrations return to normal during recovery and sometimes become higher than normal when affected children are treated with calcium-free diets, and radiologic evidence of a decrease in osteosclerosis develops.

Citrates

It has been stated that the serum citrate level is inversely related to the serum calcium.[8] In four cases studied by us no constant relationship has been found. (Table I and Fig. 3,4).

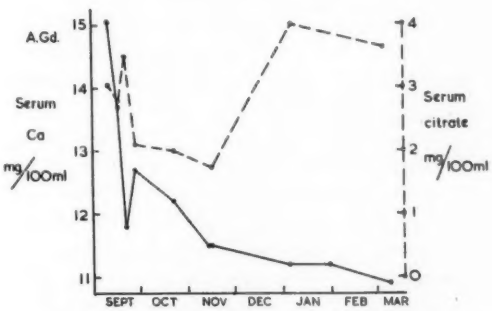

Fig. 4. The variable relationship between the serum citrate and serum calcium levels.

Urea

The blood urea is raised, although not necessarily throughout the whole active course of the disease. In some infants it is of the order of 160 to 180 mg/100 ml even in the absence of dehydration.

Vitamin A

Plasma vitamin A levels were estimated in eight infants with idiopathic hypercalcemia and were significantly higher than those found in normal infants, or in marasmic infants, both in the fasting state and four hours after a standard oral test dose of vitamin A.[14]

PATHOGENESIS

The clinical, chemical and pathologic findings closely resemble those which are found in persons who have received excessive intakes of vitamin D. (Fig. 5) The following evidence suggests that a large intake of vitamin D is a main causative factor:

(1) All infants with the disease have received vitamin D either as a supplement or in a fortified infant food.

(2) The vitamin D intake of infants in the United Kingdom, where the disease has been commonest, has increased during the past fifteen years largely as a result of the increased fortification of infant foods; the extent of this increase was not fully appreciated until recently. This is shown in the tables reproduced from the report by a sub-committee of the British Paediatric Association[15] (Tables II, III). These figures permit an approximate estimate to be made of the likely intake of vitamin D of an infant fed on the full-cream milk, referred to in Table II fortified with crystalline calciferol 460 I.U. per dry ounce, the calciferol-fortified cereal referred to in Table III, together with the generally recommended quantity of cod-liver oil compound:

For example, the vitamin D intake of an infant who receives each day

	Approximately
(a) 1½ pints of a full-cream dried milk containing 460 I.U. vitamin D per dry oz	1,725 I.U.
(b) 1 oz of a cereal containing 1,500 I.U. vitamin D per dry oz	1,500 I.U.
(c) 1 teaspoonful of national cod-liver oil compound (Welfare Food Service) would be about 4,000 I.U.	700 to 800 I.U.

(3) The disorder has occurred in Finland, especially among premature babies who have had interstitial plasma cell pneumonia. These infants had all received several hundred thousand units of vitamin D as stoss therapy.[16,17]

An excessive vitamin D intake, however, cannot be the sole factor leading to the development of the disorder, because thousands of infants in the United Kingdom and elsewhere must have received as large doses of vitamin D as those few hundreds who have developed the disease; and some infants with the disease have not received excessive doses of vitamin D. Some infants have been affected in the early weeks of life. These three facts suggest that idiopathic hypercalcemia may be due to the par-

TABLE II

The Amounts of Crystalline Calciferol Added to a Proprietary Brand of Full-Cream Dried Milk, and Reports of Assays of Vitamin D in the Milk

Date	Crystalline Calciferol added *I.U./dry oz*
Up to August 1942	70
From August 1942	128
From October 1943	403
From November 1944	460
From October 1954	690

Age of milk months	Year of manufacture	Assays
7 to 12	1950	362
13 to 18	1952	463
		405
3 to 6	1952	560

TABLE III

The Amount of Calciferol Added to a Dried Cereal and Reports of Assays

Date	Crystalline Calciferol added *I.U./dry oz*	Assays	
		Age of food months	*I.U./dry oz*
Up to March 1946	1,000		
From March 1946	2,000	0 to 2	1,110 to 1,870
		13 to 28	758 to 1,200

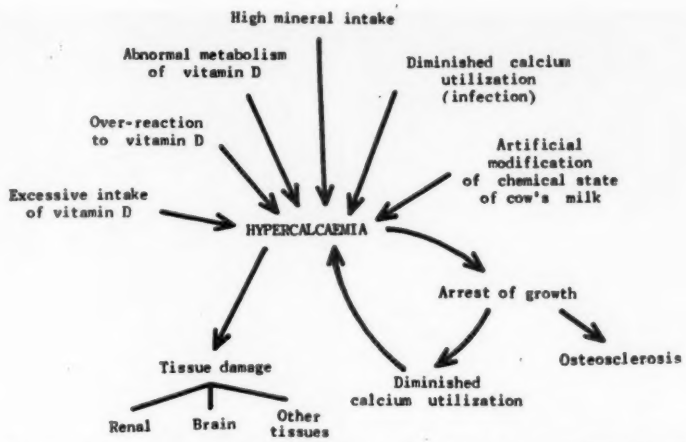

Fig. 5. The pathogenesis of idiopathic infantile hypercalcemia (Modified[38] from Helvet. Paediat. Acta 10:149, 1955.)

ticular response of some infants to vitamin D, either an extreme of the physiologic variation, or an inborn metabolic defect which causes them to react in an abnormal manner.[18,19]

The fall in the high serum calcium when cortisone is given resembles that observed in sarcoidosis with hypercalcemia.[20] In both instances, it may be caused by an anti-vitamin D effect.

Conditioning Factors

Alternatively, or in addition, there may be conditioning factors which make some infants more susceptible to a given dose of vitamin D.

(1) All the infants reported as suffering from idiopathic hypercalcemia have been artificially fed. The high calcium and phosphorus content of cow's milk (approximately 120 mg/100 ml and 95 mg/100 ml, respectively), compared to those in human milk (approximately 30 mg/100 ml and 15 mg/100 ml, respectively) must at least predispose to the development of the disease.

(2) Impaired rates of growth lower the net requirement of calcium, phosphorus and vitamin D. This was probably a factor in the infants who had had interstitial plasma cell-pneumonia reported from Finland.[16] Infections have preceded the onset of the disease in cases reported from the United Kingdom.[8,21]

(3) Idiopathic hypercalcemia has been recognized in infants in many countries (Finland, Norway, Portugal, Sweden, Switzerland, United Kingdom and United States of America). Although the vitamin D fortification of milk is much less in America than it has been in the United Kingdom, many American mothers must have given their infants supplementary vitamin preparations; the disease has not been overlooked, yet the number of cases apparently has been small. A possible explanation may be in the use of evaporated milks in the North American Continent, whereas in the United Kingdom dried milks are in general use. It has been suggested that the essential fatty acid content of dried milks may be lower than that of evaporated milks,[22] (both, of course, being cow's milk have a lower essential fatty acid content than human milk). This is an attractive hypothesis which would explain the geographic distribution of the illness, and might help to account for the high plasma cholesterol levels found in affected infants, as there is some evidence that a deficiency of essential fatty acids interferes with sterol metabolism and can be followed by a raised plasma cholesterol.[23–25] Sinclair's claim is not supported by analyses of different preparations of cow's milk for their essentially fatty acid contents.[26]

While investigating this problem we have made an interesting observation. An infant with idiopathic hypercalcemia and an infant

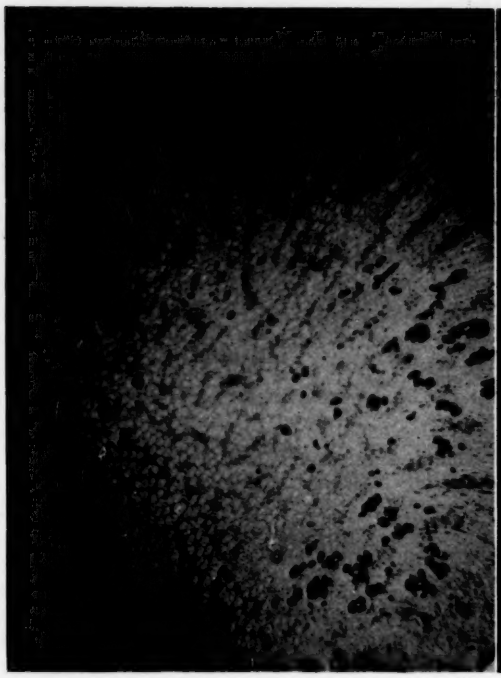

Fig. 6. Section of kidney stained for calcium from a female infant with idiopathic hypercalcemia who died at age of 11 months (no treatment having been given for comparison with Figure 7).

Fig. 7. Section of kidney from a rat six weeks old which had been given 500,000 units calciferol 12 days previously. (Alizarin × 16.)

with a normal serum calcium level were given by mouth cotton seed oil, which is rich in essential fatty acids. In both instances there was a fall in the serum calcium level, with a rebound on discontinuing the oil.

The raised vitamin A levels in idiopathic hypercalcemia[14] support the possibility of abnormal fat metabolism in this disease.

COMPLICATIONS

The complications of idiopathic hypercalcemia appear to be due to the high serum calcium, its duration of action, and the age of the infant when it develops. The type of complication is determined by the location of metastatic calcification in the body and the overall effect of calcium on tissue metabolism.

Kidneys

Renal involvement is evidenced by azotemia. Calcification and fibrosis of the kidneys have been reported by several investigators,[2,7,13,27–30] and it seems that this organ is the most constant site of calcium deposition. Calcium deposits are concentrated at the cortico-medullary junctions (Figures 6, 7), and are seen as concretions within the lumina of the tubules and as amorphous deposits in the interstitial tissue. Similar changes at this site occur in rats given toxic doses of vitamin D, and also in rats given smaller doses of vitamin D together with acetazolamide.[31]

Renal Function

The high blood urea may fall to normal limits after two to three weeks of treatment independently of hydration changes. This is in keeping with the improvement in renal function (Table IV), and resembles that which occurs in sarcoidosis with hypercalcemia following treatment.[32] It seems unlikely that kidneys with the severe damage and fibrosis seen in some

fatal cases of idiopathic hypercalcemia could improve to this extent in such a short time, and it is probable that earlier and reversible changes occur. There might be a clearing of kidney tubules obstructed by calcium casts as has been reported in vitamin D poisoning studied by renal biopsy.[33] The impaired inulin and urea clearances which improve during treatment would support this theory, unless altered permeability of tubular epithelium in this disease nullifies the clearance results. An alternative or additional explanation is that a high level of ionized calcium may inhibit enzyme activity in renal tubular cells without causing irreversible changes.

Our experiments done on young rats poisoned with vitamin D and receiving a high-calcium diet show no reduction in the oxygen uptake of kidney slices. The oxygen uptake of kidney slices of healthy young rats is not diminished by the addition of high concentrations of calcium or vitamin D to the Krebs-Ringer medium. These experiments, however, do not deny the possibility of a lesser degree of inhibition of metabolic processes not directly concerned with aerobic oxidation, but with more specialized organ function.

Vitamin D in its soluble phosphorylated form is an activator of aerobic oxidation in tissues other than bone, as well as being an activator of other enzymes such as alkaline phosphatase.[34] Thus it is reasonable to assume that if a depression of tissue metabolism occurs in hypercalcemia it is more likely to be due to the hypercalcemia than to a primary vitamin D effect.

Other Sites of Calcification

Calcification of blood vessels[27] of the myocardium and heart valves[13,29] and in subcutaneous tissues[35] have been described. Osteosclerosis is a common feature in the more severe grades of the illness. Calcification has also been found in the lungs and the fundal glands of the stomach.[13]

The systolic murmur which is frequently found in affected infants may be due to calcification in cardiac valves, the hypertension to thickening or calcification of arterial walls.

TABLE IV

Renal Function Tests*

C. Hm. (Female)

Age in Months	Serum calcium mg/100 ml	Blood urea mg/100 ml	Urine specific gravity	Inulin clearance						Urea clearance						Urea clearance-inulin clearance ratio
				U mg/100	V ml	P mg/100 ml	Time mins	Uncorrected ml/min	Corrected To surface area 1.73 M² ml/min	U mg/100	V ml	P mg/100 ml	Time mins	Uncorrected ml/min	Corrected To surface area 1.73 M² ml/min	
10	13.4	70	1.014 (19 hr)	391	57.5	58	60	6.5	34	465	57.5	71	60	6.3	33	1.03
				540	49	63	60	7.1	37	565	49.0	69	60	6.7	35	1.05
10½	12.0	68	1.010 (14 hr)	300	63	33	82	7.0	37	565	63	68	82	6.4	33	0.90
13	11.2	58	1.022 (18 hr)	398	62	29	70	12.1	56	550	62	58	70	8.4	39	0.69
				413	64	30	60	14.9	70	470	64	58	60	8.6	40	0.58
20	10.8	42	1.022 (15 hr)	222	112	18	60	23.0	83	410	112	46	60	16.6	60	0.72
				616	54	16	70	30.1	108	860	54	46	70	14.4	52	0.47

* The clearances were done when the infant was sedated with a barbiturate. The urine volumes include the 30 ml. water used for bladder washings.

Note the low inulin and urea clearances in the severe stage of the disease, with an improvement and fall in the urea/inulin clearance ratio when the serum calcium fell.

TREATMENT

The efficacy of treatment depends on the stage of the illness at which it is given. Some infants with hypercalcemia recover without special treatment. On the other hand, some of the severely affected infants have changes which are largely irreversible. In most cases, recovery can be accelerated by treatment. The chief methods of lowering the serum calcium are (1) a low-calcium diet, and (2) cortisone.[4-6,8,9,36-38]

A low-calcium diet is the mainstay of treatment.[9,36] This can be in the form of a low-calcium milk, produced either by treating cows' milk with a calcium-free ion exchange resin,[39,40] or as a commercial dried milk preparation, Locasol (Trufood) containing 7 mg calcium per 100 ml of reconstituted whole milk. In addition, older infants can be given a low-calcium cereal (Glaxo)—containing approximately 0.1 mg of calcium per gram of cereal. This cereal with its low-calcium content and its high inorganic phosphorus and phytate content results in an appreciable negative calcium balance due to a high content of calcium in feces.[5,9,37]

Low-calcium cereal has the added advantage of a high caloric value so that weight gain is better (and this may be an important factor in accelerating cure if calcium utilization improves). For infants who are entirely bottle fed it can be added to the milk in small amounts (up to a drachm per ounce has been found satisfactory).

The disadvantage of the low-calcium diet is that the preparation of the low-calcium milk and cereal, to be fully effective, requires the use of water of low-calcium content. In certain areas, this means distilled water.

The response of the serum calcium level to diet is not always quick and it may be desirable to give cortisone. Given orally in doses of 25 to 50 mg per day, it results in a fall in serum calcium within a few days. The effect is not permanent, as on discontinuing the cortisone, the serum calcium may rebound to a high level.[5] The main value of cortisone is its use as a short term form of therapy combined with the low-calcium diet. After two to four weeks it can be discontinued, by which time the calcium-lowering effect of the diet should be well established.[9] Used over long periods there is the risk of undesirable side effects such as hyperadrenocorticism, and masking of intercurrent infections.

The mode of action of cortisone is not understood, although its main effect appears to be in blocking absorption of calcium from the bowel. The administration of cortisone to infants with idiopathic hypercalcemia[4,5] and adults with sarcoidosis[20] results in negative calcium balances from fecal losses. Its structural similarity to vitamin D has prompted the suggestion of competition for substrate.[20]

It is important that infection should be avoided as much as possible, and if contracted, it should be promptly treated, especially if the infant is on cortisone therapy.

Other measures have been used to limit calcium absorption from the bowel. There have been no reports of phytates being used alone for the treatment of hypercalcemia in infants, but they have been used in the treatment of hypercalcemia in sarcoidosis in adults.[41] There seems to be no contraindication to their use in infants and they should increase the fecal loss of calcium if added to the low calcium diets. The disodium salt of ethylene diamine tetra acetic acid has been used as a calcium-extracting agent.[4] We believe that this treatment carries a serious risk[42] and consider it unnecessary in view of the effectiveness of other forms of treatment.

It is possible that vegetable oils containing high percentages of essential fatty acids may have some use in idiopathic hypercalcemia.

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REFERENCES

1. LIGHTWOOD, R.: Idiopathic hypercalcaemia in infants with failure to thrive. *Arch. Dis. Childhood* 27: 302, 1952.
2. FANCONI, G., GIRARDET, P., SCHLESINGER, B., BUTLER, N., and BLACK, J.: Chronische Hypercalcämie, combiniert mit Osteosklerose, Hyperazotämie, Minderwuchs und kongenitalen Miss-

bildungen. *Helvet. Paediat. Acta* 7: 314, 1952.
3. CORDEIRO, M.: Hipercalcemia idiopatica. *J. Med. Porto* 28: 483, 1955.
4. MORGAN, H. G., MITCHELL, R. G., STOWERS, J. M., and THOMSON, J.: Metabolic studies on two infants with idiopathic hypercalcaemia. *Lancet* 1: 925, 1956.
5. MACDONALD, W. B., and STAPLETON, T.: Idiopathic hypercalcaemia of infancy. Studies of the mineral balance. *Acta Paediat.* 44: 559, 1955.
6. CREERY, R. D. G., and NEILL, D. W.: Idiopathic hypercalcaemia in infants with failure to thrive. *Lancet* 2: 110, 1954.
7. LOWE, K. G., HENDERSON, J. L., PARK, W. W., and MCGREAL, D. A.: The idiopathic hypercalcaemic syndromes of infancy. *Lancet* 2. 101, 1954.
8. FORFAR, J. O., BALF, C. L., MAXWELL, G. M., and TOMPSETT, S. L.: Idiopathic hypercalcaemia of infancy. Clinical and metabolic studies with special reference to the aetiological role of vitamin D. *Lancet* 1: 981, 1956.
9. STAPLETON, T., MACDONALD, W. B., and LIGHTWOOD, R.: Management of "idiopathic" hypercalcaemia in infancy. *Lancet* 1: 932, 1956.
10. LIGHTWOOD, R.: Idiopathic hypercalcaemia. *Rev. Port. Pediat. e Puericult.* 18: 335, 1955.
11. STAPLETON, T.: The response of idiopathic renal acidosis to oral sodium lactate. *Acta Paediat.* 43: 49, 1954.
12. PAYNE, W. W.: The blood chemistry in idiopathic hypercalcaemia. *Arch. Dis. Childhood* 27: 302, 1952.
13. SCHLESINGER, B. E., BUTLER, N. R., and BLACK, J. A.: Severe type of infantile hypercalcaemia. *Brit. M. J.* 1: 127, 1956.
14. FYFE, W. M.: Vitamin-A levels in idiopathic hypercalcaemia. *Lancet* 1: 610, 1956.
15. British Paediatric Association Report. Hypercalcaemia in infants and vitamin D. *Brit. M. J.* 2: 149, 1956.
16. HALLMAN, N.: Calcium metabolism in interstitial plasma cell pneumonia in infants. *Helvet. Paediat. Acta.* 10: 119, 1955.
17. HJELT, L., AHVENAINEN, E. K., and HALLMAN, N.: Renal calcification in infancy. Autopsy findings in interstitial plasma cell pneumonia and other pathological conditions. *Ann. Paediat. Fenn.* 2: 169, 1956.
18. LIGHTWOOD, R., and STAPLETON, T.: National policies for the prevention of rickets. *Ann. Paediat.* 188: 270, 1957.
19. ZETTERSTRÖM, R.: Quoted in discussion. Internationales Elektrolyt-symposium. *Helvet. Paediat. Acta* 10: 149, 1955.
20. ANDERSON, J., DENT, C. E., HARPER, C., and PHILPOT, G. R.: Effect of cortisone in sarcoidosis with hypercalcaemia: possibly antagonistic actions of cortisone and vitamin D. *Lancet* 2: 720, 1954.
21. CREERY, R. D. G., and NEILL, D. W.: Infection in the etiology of infantile hypercalcaemia. *Lancet* 2: 1357, 1956.
22. SINCLAIR, H. M.: Infantile hypercalcaemia. *Lancet* 2: 893, 1956.
23. BRONTE-STEWART, B., ANTONIS, A., EALES, L., and BROCK, J. F.: Effects of feeding different fats on serum cholesterol level. *Lancet* 1: 521, 1956.
24. SINCLAIR, H. M.: Deficiency of essential fatty acids and atherosclerosis, etcetera. *Lancet* 1: 381, 1956.
25. KEYS, A., ANDERSON, J. T., and GRANDE, F.: "Essential" fatty acids, degree of unsaturation, and effect of corn (maize) oil on the serum cholesterol level in man. *Lancet* 1: 66, 1957.
26. JAMES, A. T.: Personal communication, 1957.
27. LIGHTWOOD, R.: A case of dwarfism and calcinosis associated with widespread arterial degeneration. *Arch. Dis. Childhood* 7: 193, 1932.
28. DAWSON, I. M. P., CRAIG, W. S., and PERERA, F. J.: Idiopathic hypercalcaemia in an infant; clinical and post mortem findings in one case. *Arch. Dis. Childhood* 29: 475, 1954.
29. HJELT, L., TAHKA, H., and HALLMAN, N.: Chronic hypercalcaemia and vitamin D in early childhood. *Ann. Paediat. Fenn.* 2: 75, 1956.
30. RHANEY, K., and MITCHELL, R. G.: Idiopathic hypercalcaemia of infants. *Lancet* 1: 1028, 1956.
31. HARRISON, H. E., and HARRISON, H. C.: Inhibition of urine citrate excretion and the production of renal calcinosis in the rat by acetazoleamide (Diamox) administration. *J. Clin. Investigation* 34: 1662, 1955.
32. DENT, C. E., FLYNN, F. V., and NABARRO, J. D. N.: Hypercalcaemia and impairment of renal function in generalized sarcoidosis. *Brit. M. J.* 2: 808, 1953.
33. BJORNEBOE, M., BRUN, C., IVERSEN, P., GORMSEN, H., and RAASCHOU, F.: Two cases of calcinosis renis, studied by means of renal biopsy and renal function tests. *J. Clin. Investigation* 31: 727, 1952.
34. ZETTERSTRÖM, R.: Phosphorylation of vitamin D_2 and the action of the phosphorylated compound on alkaline kidney phosphatase. *Nature* 167: 409, 1951.
35. CLAY, P. R.: Idiopathic hypercalcaemia with subcutaneous calcium deposits following pseudosclerema. *Proc. Roy. Soc. Med.* 49: 598, 1956.
36. RUSSELL, A., and YOUNG, W. F.: Severe idiopathic infantile hypercalcaemia. Long term response of two cases to low calcium diet. *Proc. Roy. Soc. Med.* 47: 1036, 1954.
37. BONHAM CARTER, R. E., DENT, C. E., FOWLER, D. I., and HARPER, C. M.: Calcium metabolism in idiopathic hypercalcaemia of infancy with failure to thrive. *Arch. Dis. Child.* 30: 399, 1955.
38. STAPLETON, T., and EVANS, I. W. J.: Idiopathic

hypercalcaemia in infancy. *Helvet. Paediat. Acta* 10: 149, 1955.

39. FERGUSON, A. W., and MCGOWAN, G. K.: Idiopathic hypercalcaemia of infants: low-calcium treatment. *Lancet* 1: 1272, 1954.
40. DENT, C. E.: How to make decalcified milk. *Helvet. Paediat. Acta* 10: 165, 1955.
41. HENNEMAN, P. H., CARROLL, E. L., and ALBRIGHT, F.: The suppression of urinary calcium and magnesium by oral sodium phytate: a preliminary report. *Ann. New York Acad. Sc.* 64: 343, 1956.
42. LIGHTWOOD, R.: Treatment of Idiopathic Hypercalcaemia. *Brit. M. J.* 2: 304, 1954.

Studies on Phenylketonuria

IX. FURTHER OBSERVATIONS ON THE EFFECT OF PHENYLALANINE-RESTRICTED DIET ON PATIENTS WITH PHENYLKETONURIA

By MARVIN D. ARMSTRONG, PH.D.,* NIELS L. LOW,† M.D., AND JAMES F. BOSMA, M.D.‡

RECENTLY there have been reports from several laboratories concerning the effects obtained by administering phenylalanine-restricted diets to patients with phenylketonuria.[1–8] This type of regimen has been found to correct the major biochemical abnormalities which are present in phenylketonuria. In addition it has been apparent that improvement has occurred in the clinical condition of some, though not all, of the patients who have been studied. The purpose of the present publication is to present follow-up studies on patients reported previously,[3] to record observations on new patients, and to discuss the observations with regard to the possible manner of development of the mental and neurological impairment present in phenylketonuria.

DIETARY MANAGEMENT

For the clinical studies subsequent to those previously reported,[3] a properly supplemented phenylalanine-deficient casein hydrolysate has been used, rather than a mixture of pure amino acids. The major differences between the composition of the amino acid mixture[3] and the supplemented casein hydrolysate are that in the latter there are: (1) the presence of a relatively lower amount of aspartic acid (rather than asparagine), (2) the presence of proline and serine, (3) altered relative levels of many amino acids, and (4) the inclusion of both DL-tryptophan and L-tyrosine at considerably higher levels. The basal mix prepared from the supplemented casein hydrolysate contained appropriate minerals, but no water-soluble vitamins; these were administered daily in the form of commercial preparations. Proportions of amino acids, carbohydrates, fat and total calories were adjusted as described earlier.[3]

Nutritional difficulties which arise from continued use of the synthetic diet were minimized by allowing higher blood levels of phenylalanine than were maintained during the previous study. After the initial depletion period, an estimated 25 mg of phenylalanine per kg body weight per day in the form of natural protein has been found to result in a serum phenylalanine level of 4 to 8 mg per 100 ml for most cases.* This level of phenylalanine is well below that which leads to the formation of phenylpyruvic acid in amounts large enough to be detected in the urine.[9] Since the earlier detailed studies had demonstrated that it is possible to maintain low blood phenylalanine levels and to eliminate the abnormal urinary metabolites, frequent analytic data were not obtained with the present cases. After the appropriate intake of natural protein had been established with each patient, measurements of blood phenylalanine levels were made at intervals of a month or longer. Further and

From the Laboratory for the Study of Hereditary and Metabolic Disorders, and the Departments of Pediatrics, Biological Chemistry, and Medicine, University of Utah College of Medicine, and the Utah State Health Department, Salt Lake City.

* Associate Research Professor, Biochemistry, University of Utah.

† Associate Research Professor, Pediatrics, University of Utah.

‡ Professor, Pediatrics, University of Utah.

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* It should be noted that the modification of the method of Kapeller-Adler used in this laboratory[3] does not give accurate values. The same reproducible procedure has been used throughout this work, however, and the values are consistent.

more detailed information on the dietary management of patients will be reported elsewhere.

CLINICAL PROCEDURES

In general pediatric observations, the patients were found to demonstrate essentially normal somatic growth and gross bodily proportions, aside from relative microcrania in one infant, and occasional distortions of head and trunk which probably had resulted from general bodily immobility. The skin was found to be soft and the subcutaneum lax. A chronic, superficial inflammatory reaction demonstrated by erythema and fine scaling was apparent in some children. This inflammatory reaction was increased in areas of abrasion, such as the cheeks, and in areas of chemical irritation, as under the diaper. Plethora of palms and soles was of normal distribution but diminished in degree. There was commonly a fine vascular mottling of the skin of the trunk and extremities. No abnormality of nasal, oral, or pharyngeal mucosae was seen. The skin and subcutaneum of the trunk and limbs were readily penetrated by a Number 22 or 24 needle and the limb veins tore easily incident to venipuncture, so that ecchymosis occurred commonly. The musculature was diminished in mass, soft and lax, and articular support was generally deficient.

For an evaluation of the initial neurologic effects of dietary therapy on these subjects, observations of their seizure disorder were of special importance. In addition, their duration of attention, irritability, or calmness under stimulation, and their effective response were found to be useful criteria. For the periodic observations made during prolonged dietary therapy, particular increments of achievement were noted and the general developmental level was estimated.

The seizure disorder of the infant subjects was manifested most commonly by the comparatively subtle clinical phenomena of lapses and brief jerks, variably distributed in the trunk and extremities, which have been termed "infantile spasms."[10] This form of seizure disorder, which is commonly overlooked clinically, is found not infrequently in infants and small children who suffer diffuse neurologic impairment. It is associated characteristically with hypsarhythmia, as described by Gibbs *et al.*[10] in the electroencephalogram. The frequent occurrence of seizures in phenylketonuria, particularly in infants, has been pointed out previously by Ford[11] and by Low *et al.*[12]

PATIENT DATA

F. D. (Case 1,[3] Case 6.[12]) (Born Nov. 13, 1947.) This was the case of a red-haired, blue-eyed girl who was able to sit without support at one year and started walking at two years. She is said to have used a few words at one year but to have lost that ability during her second year. At age four and one-half years she was given a phenylalanine-restricted diet for 12 weeks. After a seeming initial improvement in attention span, she regressed to the same level of behavior and activity after three months as before treatment was started. During that period, however, her eczema disappeared. When her diet was discontinued, the eczema recurred but no other striking changes were observed. She was admitted to the Utah State Training School in 1956. At the present time she is a stout girl who has mild eczema in the flexor areas and at the ankles. She walks with poor balance and a wide-based gait. She can repeat a few single words in a parrot-like fashion. She is still very distractible and spends much of her time sitting on the floor, grinning or shouting. In general, she appears to have progressed at a consistently slow rate after the first year or two of life. The degree of retardation did not appear to be so severe during the first year.

A. Du. (Case 2,[3] Case D.[12]) (Born July 8, 1948). This boy apparently developed normally for the first five months of life; regression of performance became apparent after an ear infection at that age. When seven months old he began to have frequent seizures. He continued to have a severe seizure disorder and made little neurologic progress. At the age of 48 months he showed increased muscular tone and his tendon reflexes were hyperactive and equal; he did not have eczema. He paid no attention to persons or objects, and was not able to sit up. Phenylalanine-restriction was then commenced. While he was receiving the diet, and with no anticonvulsant medication, his seizures stopped; phenobarbital had not controlled them previously. His EEG became normal and remained so for some time after the diet was discontinued. His seizures have not recurred although the EEG again showed seizure discharges.[12] The restricted diet diminished his tremor when excited, improved his neurologic abnormalities, and improved his attention span.

During the succeeding four years he has continued to develop at an extremely slow rate. Now, at the age of eight and one-half years, he has begun to pull himself into a standing position in his crib. He still shows no affective response to persons and no interest in objects. He spends most of his time in bed in grotesque positions, chewing, biting, and drooling.

J. Du. (Case 3,[3] Case C.[12]) (Born July 3, 1951.) This child, a sister of A. Du, developed eczema at the age of five months which is still present at five and one-half years of age. She sat without support when six months old, pulled herself to standing when 10 months old, and walked with slight support at the age of one year. A marked tremor was apparent before she was one year old, particularly when she was excited or tired. She was maintained on a phenylalanine-restricted regimen from the age 13 to 23 months. During this 10-month period she appeared to develop at a fairly normal rate. Her eczema was absent during that period. Her tremors diminished. At the age of 23 months psychometric evaluation (Kuhlman test) indicated a mental age of 18 months (I. Q. 78). For a few months after treatment was discontinued she seemed to maintain her abilities, but after 14 months she was estimated to have gained only five months of mental age (I. Q. 67); in retrospect, it was suggested that the testing circumstances had not been favorable. When 47 months old she was estimated by the same psychologist, this time with the Stanford-Binet test, to perform at a 38-month level (I. Q. 83).

In February 1957 (age five years, seven months), the child was re-examined. Her speech was somewhat infantile, although her vocabulary corresponded to her chronologic age. She dressed herself completely, except for tying her shoes and tying a bow on the back of her dress. Psychologic evaluation showed her to have a development quotient of 97. Although she could draw pictures and geometric patterns spontaneously on the five to six year level, she was unable to copy the same patterns when presented with a sample. No tremors were observed on that visit.

The only EEG recorded, when patient was three years of age, showed a few parietal and occipital spikes.

This child suffered less neurologic damage at an early age than did the other patients in this series. There was no evidence of deterioration after the first two years of life, but rather an apparent increase in intellectual ability, as indicated by psychometric evaluation.

M. J. (Case 4,[3] Case A.[12]) (Born August 9, 1953.) This girl was first seen at the age of nine and one-half months. She had been hospitalized at the Colorado General Hospital when approximately three months of age because of a severe acute illness with pneumonia, diarrhea, dehydration, and acidosis. At that time she had been observed to be neurologically prostrated and had had a prolonged left-sided convulsion. Her cerebrospinal fluid protein at the time of acute illness varied from 96 to 136 mg/100 ml. Her cranial circumference at five months of age was 34.5 cm. A psychologic evaluation at that time estimated her motor development to be at the 12-week level, and her language-social functioning at the four-week level. The infant was maintained in the Metabolic Ward, Salt Lake County General Hospital, for approximately ten months, beginning at nine and one-half months of age. At admission she was small, with a cranial circumference of 39 cm. She was pale, blond, had lax skin, and generally poor muscle tone.

The infant had numerous infantile spasms[10] consisting of abrupt, single jerks of varied distribution within trunk or extremities. Her orientation to personal and object environment was insignificant. Motions of neck, trunk, face, tongue, and extremities were random in character and commonly repetitive. Limb motions were undirected and ineffectual except for the performance of repetitive clenching of fists. The general level of orientation of the infant was equivalent to that of two to three months of normal schedule of development, though in a distorted pattern. Eye coordination was essentially binocular. Posture of head upon shoulder was poor. Biceps and triceps reflexes were normal and symmetrical. Patellar reflexes were increased without elicitation of clonus. The plantar reflexes were in extensor pattern. Suckle and swallow were accomplished in normal fashion, and there was no pharyngeal pool. An EEG obtained at this time demonstrated continuous hypsarhythmia.

The infantile spasms became progressively less evident, and she became more active and vigorous after initiation of the phenylalanine-restricted diet. She responded to attention and demonstrated an elementary smile. After three weeks she reached for objects and minimal posture was developed in the neck and upper trunk. She showed increasing visual attention and would follow objects carried into the superior visual field. With acquisition of visual attention a convergent strabismus was noted for the first time. The plantar reflexes became asymmetrical three weeks after the diet was initiated, the left converting to flexor and the right persisting in extensor pattern.

As reported heretofore,[3] the infant's accelerated progress continued during the first three months of phenylalanine restriction. In the following weeks, however, it became apparent that this rate of development was not being maintained. She remained consistently free of outward signs of seizures and her EEG was improved, but it continued to show intermittent hypsarhythmia. After five months she showed questionable recognition of a ward aide who gave her much attention. Her responsive smile continued to be vague, brief, and was supplemented with minimal simple phonations which were similar to those she uttered spontaneously when alone. She began to show visual awareness of objects and occasionally studied her hands. She would grasp objects and hold them in an unpurposeful manner before discarding them. At this time she was able to raise herself from supporting surface on hand and pelvis and could sit with support. Startle reactions continued to be marked and the infant would assume an opisthotonic position on abrupt stimulation. Patellar reflexes continued to be maximal and occasionally a brief clonus was elicitable.

Since it became apparent that this infant was not showing the sustained progress that R. Du. maintained, and that she probably had suffered extensive irreversible damage, the effect of restoring her previous high blood phenylalanine level was tested. At the age of 15 months, after five months of phenylalanine restric-

tion, an EEG was made while patient was sleeping and while awake, 4 g of L-phenylalanine was given to her via stomach tube, and the EEG was recorded for the ensuing four hours. Her serum phenylalanine level was 7 mg/100 ml just prior to administration of the phenylalanine and 63 mg/100 ml 90 minutes after it was given. No significant change in the EEG was noted during the entire period nor the following day. For the next six weeks 2.4 g of L-phenylalanine was added to her diet daily. Her fasting serum phenylalanine level was 61 mg/100 ml. At the end of this time no striking deterioration had occurred, but she had lost some of her previous attainments; i.e., no longer attempted to stand on her head or sit up, seemed crosser and less alert, and demonstrated some tremulousness of her hands.

Her daily intake of L-phenylalanine was then increased to 5 g; this led to a serum phenylalanine level of 80 mg/100 ml. With this higher intake of phenylalanine her condition worsened rapidly. After five weeks she was very pale, lay immobile and almost comatose, with neck and trunk stiff, and with motion, when undisturbed, limited to arms and hands. Her EEG became markedly worse, but outward signs of seizure did not reappear.

Phenylalanine was again withdrawn from the child's diet at the age of 17 months; in 2 weeks the serum phenylalanine decreased from 80 to 2 mg/100 ml. She recovered very rapidly from the deteriorated condition, and within ten days appeared to be as alert and to have as many capabilities as at 14 months, when phenylalanine had been restored to her diet. She was maintained on a phenylalanine-restricted diet for the following three months in Salt Lake City and in Denver, Colorado. Little further change in her condition was observed during this time, and the restricted regimen was discontinued.

The patient was lost to follow up for 18 months, but then had a psychologic evaluation at the University of Colorado Medical Center in September 1956, at the age of 37 months. At that time she functioned at an eight to nine month level in all four areas of development according to the Gesell Scale. She was able to sit up but made no attempt to support herself when put into a standing position. She showed no interest in people; she could hold her bottle and feed herself crackers. According to her mother, she could say "mama" and "dada." Her fasting serum phenylalanine level at that time was 50 mg/100 ml.

This child had suffered extensive brain damage before dietary treatment was initiated. This severe neurologic involvement was evidenced by microcrania, convulsions, and elevated cerebrospinal fluid protein. Whether this initial disease was related to phenylketonuria or not is not clear, but it limited any possible improvement that could be obtained on the phenylalanine-restricted regimen.

R. Du. (Case 5,[3] Case B.[12]) (Born Sept. 12, 1953). A brother of A. Du and J. Du, the development of this boy for the first seven months of life was considered essentially normal with good quality of alertness interpersonal recognition and discrimination, appropriate phonation, intra-oral manipulation, reach, grasp, and posture. The first evidences of simple tonic seizures were detected incident to an illness in the seventh month. These progressed within a few days to repetitive grand mal episodes. There was coincident indolence, diminution in interpersonal recognition and response, and loss of motor achievement. An EEG at that time demonstrated continuous hypsarhythmia (Fig. 2).[12]

A phenylalanine-restricted diet was initiated at seven and one-half months of age. The minor motor seizure phenomena became less frequent, but typical major grand mal pattern appeared; these major seizures occurred approximately three to five per day the first week following initiation of diet and subsequently diminished progressively to termination within three weeks. Coincident with this change in seizure pattern the boy became more alert and calm and gradated more stably into and from sleep. At the end of one month the first evidences of return of affection response appeared. Gross motor achievement progressed rapidly from his immediate pretherapy status of comparative neurologic failure. Within three weeks of initiation of the diet he sat with support of his hands and attempted to crawl; coincidentally, muscular tightness observed in the neck and trunk were relieved without other therapy. Binocular following of large test object increased in range to far lateralward gaze toward either side. Motions of extremities retained an abnormal abrupt and irregular quality. The EEG improved steadily and after five weeks showed no signs of abnormality (Fig. 3).[12]

Because of the striking improvement in seizure disorder and EEG, the effect on the EEG of restoring a high blood level of phenylalanine was tested. A control EEG was recorded, 6 g of L-phenylalanine was administered by stomach tube, and the record was continued for four hours. Serum phenylalanine level was 2 mg/100 ml before, and 88 mg/100 ml 90 minutes after administration of the amino acid. There were no significant alterations in his EEG either immediately or during the following two weeks. During this time he received 0.85 g of L-phenylalanine daily and had a fasting serum phenylalanine level of 35 mg/100 ml. His behavior during this period has been described earlier.[3]

The phenylalanine-restricted diet was resumed, beginning again when patient was 10 months old and continuing until the age of 29 months. The adequacy of the dietary regimen in controlling serum phenylalanine was established by frequent assays of urine samples for *o*-hydroxy-phenylacetic acid,[13] and less frequently by direct measurements of serum phenylalanine. The child maintained levels of less than 10 mg/100 ml of phenylalanine except on two occasions, at the age of 12 and 29 months, when 15 mg/100 ml was observed. No phenylpyruvic acid could be detected in his urine during the entire period. His health remained good,

and he gained in weight from 19 lb to 26½ lb, in height from 18½ in. to 35 in. and in cranial circumference from 44.5 cm to 47 cm.

Developmentally, the child followed an almost normal pattern, lagging behind slightly. At the age of 12 months he walked with support and at 14 months of age he walked without help; he also employed meaningful sounds. When 16 months old he engaged in mimicry, balked, climbed adeptly, and had manual dexterity equivalent to 14 months of usual schedule. A psychometric examination at the age of 25 months (Stanford-Binet, Cattell) indicated an I. Q. of 82, and another when 29 months old, I. Q. 80. The EEG at 29 months appeared to be normal.

At this time the restricted regimen was discontinued and the boy was allowed to eat a natural diet. He continued to develop at the same slightly retarded schedule for the next year. Psychometric evaluation showed an I. Q. of 86 at 33 months and 83 at 42 months. The EEG showed a few spikes at 33 months, but a waking and sleep record at 42 months was normal. There has been no indication of deterioration in the year he has been receiving a natural diet. When 36 months old, his fasting serum phenylalanine was 45 mg/100 ml.

S. L. (Case H.)[12] (Born Jan. 15, 1952.) This girl was born of normal pregnancy and delivery and appeared to be normal in the period immediately following birth. Her early developmental progress was on a retarded schedule; the mother first realized the child was retarded at the age of approximately six months. She sat without support at approximately 11 months of age. Since she attained the age of 12 months, she had episodes of "staring," but had no overt grand mal seizures.

Upon initial observation at the age of 35 months this child was seen to have episodes of lapses of awareness. Her general level of performance was equivalent to that of 11 to 12 months of the usual schedule of development. She was able to distinguish her mother from others. She did not participate in dressing. She showed only minimal interest in objects, which included a familiar doll. She was able to sit without support but required help to stand or walk. Her mouth was relatively pendant with oral pool and intermittent drooling. Intra-oral manipulation was crude. There was a small variety of phonations. Her EEG showed frontal and parietal spikes.[12] Fasting serum phenylalanine level was 32 mg/100 ml.

A phenylalanine-restricted diet was initiated at the age of 36 months. The parents noted a distinct improvement in alertness and in general quality of activity for the first two weeks, but relatively little subsequent improvement. When she was next seen at the age of 42 months, there had been little change in quality of attention and no distinguishable improvement in affective response. She could sit more stably but stance and gait still required support. Variety of phonations was slightly increased. There was no distinct change in manual manipulation. There was no improvement in the EEG.

When seen again at 48 months of age, she demonstrated increased interpersonal discrimination and preference of a familiar toy. She had developed an increased empathic relationship with her mother with moderate resistance at times. She was able to raise herself to a standing position, but still required support in gait. There was a further increase in variety of phonations and she had one word of consistent meaning. Manual manipulation had improved somewhat and she would use one object to impel another. Her jaw remained relatively pendant. The clinical impression that this child underwent little change in her mental status was borne out by the result of psychometric testing. Results obtained with a battery of tests at 36, 42, 48, and 52 months showed developmental quotients of 24 to 25, 22 to 24, 21 to 23, and 18, respectively.

N. P. (Case 6.[12]) (Born Sept. 2, 1953.) This boy was born at term of a normal pregnancy and delivery. His performance was considered to be entirely normal for the first month of life, but in the second and third months he became increasingly indolent, and markedly obese. At the age of eight months he was unable to sit and would not hold objects in his hand. At this time the mother first noticed seizures in the form of abrupt flexion of the trunk on occasions of startle. When 13 months old the seizures became more frequent and prolonged and were associated with up-turning of the eyes. An EEG revealed hypsarhythmia. Subsequent development was at a very slow rate. At the age of 20 months he was able to raise himself to sitting position and to sit without support.

Initial observation by this group was when the patient was 26 months old. This child was found to demonstrate little somatic abnormality aside from symmetrical muscular stiffness in trunk and limbs. He was extremely pale and was continually restless and irritable. Interpersonal and object discrimination was poor. He was able to sit very briefly and precariously without support. He demonstrated minimal co-operation in feeding. There were few intentional phonations and there was no distinguishable utilization of hands. General level of performance was appropriate to five to seven months of usual schedule of maturation. The EEG showed continuous hypsarhythmia. Fasting serum phenylalanine level was 87 mg/100 ml.

A phenylalanine-restricted regimen was initiated at 27 months of age. He was seen again nine days later. The parents reported that he had become more calm, consistent, and responsive, and that gradation into sleep was accomplished more stably. On observation, the infant was found to be less irritable. He demonstrated an improved affective relationship with his mother. The originally noted tightness in limbs was diminished. Motor tonus was improved in neck and upper trunk, and there was noted a greater awareness of objects placed in his hands There was also a greater variety of elementary sounds.

At the next observation, age 28½ months, the parents reported that the boy had continued to have three

to four grand mal seizures per day which were characteristically brief; in addition, he had 12 to 20 infantile spasms daily. There was no further increment in improvement beyond that observed at the previous visit.

Five months later he was able to sit without support but with the back and shoulders rounded. He had generalized convulsions approximately every two to three weeks and a few infantile spasms daily. He reached for objects held before him but did not grasp them. He paid no more attention to people than previously. His EEG was unimproved. The restricted diet was discontinued at the age of 34 1/2 months.

In the next seven months he gained seven pounds. After he was taken off the diet, he continued to have four to five convulsions every three to four weeks and his minor motor seizures were observed many times daily. At the age of 41 months he still made no attempt to support himself on his legs; he reached for toys and touched them but did not grasp or pick them up. The EEG showed multiple spike foci and definite petit mal variant, especially in the frontal areas, in addition to hypsarhythmic seizure discharges. At age 42 months his fasting serum phenylalanine level was 39 mg/100 ml; the decrease in blood phenylalanine with increasing age has been commented upon elsewhere.[9]

This child showed only slight improvement during the first weeks after treatment had been started at 27 months. No appreciable improvement, beyond the one expected without the restricted diet, was noted during the last six months on the regimen.

D. W. (Case E.[12]) (Born Nov. 5, 1953.) This girl was born at term, of a normal pregnancy. When two weeks old the mother had noticed some rigidity during feeding; this persisted for several months and was of sufficient degree to occasion difficulty in dressing the baby. This infant's retardation was first suspected by the mother at five months of age, and she was taken to a pediatrician when nine and one-half months old. He observed the infant's performance at that time to be equivalent to approximately six months of usual development; there was little further increment in achievement at the age of 11 months. The child sat without support when 16 months old; when 17 months old her physician considered her performance equivalent to that of an infant seven to eight months of age of usual schedule of maturation. The mother had observed that at ten months the eyes occasionally turned abruptly upward but there was no other suggestion of recognized seizures.

She was first seen at the age of 22 months. General examination showed no significant evidence of abnormality other than neurologic impairment. The general level of orientation and response was equivalent to approximately eight months of usual schedule of maturation. There was little interpersonal discrimination. Attention to a test object was brief, and she prehended with arc-like raking motions. There was no discrete thumb-finger prehension. Intra-oral manipulation was minimal, and there was no distinguishable bite. An EEG showed multiple spike foci.[12] The diagnosis of phenylketonuria was made at this time; fasting serum phenylalanine level was 70 mg/100 ml.

A phenylalanine-restricted diet was initiated at the age of 22 months. In the succeeding three weeks, interpersonal orientation increased strikingly and responses of displeasure appeared. Object orientation and toy handling increased slightly. There was an increasing variety of phonations but they were still in elementary pattern. Posture stability increased and she was able to sit without support but was not able to bring herself into sitting position.

When the patient was 26 months old slight further improvement was evident as demonstrated by increased duration of attention and greater variety of empathic responses. She repetitively handled simple noise making toys. Posture achievement increased somewhat in that she was able to rise to sitting position and attempted to walk when supported.

At the age of 29 months, further increment in orientation was manifested in that she was able to recognize her mother and was aware of her absence when she was away from home. She now had favorite toys, her attention was more prolonged, and she laughed. Discrete intramanual coordination had further matured and was equivalent to 15 to 18 months of usual schedule of maturation. Posture achievement was increased and she was able to raise herself to standing and to walk better, though she still required support.

When 32 months of age, the patient enjoyed toys more than she had before, and when played with laughed frequently. She had started mimicking various actions, such as coughing and blowing the nose. She attempted to make appropriate use of a hairbrush or a handkerchief. She walked around furniture without help and along the wall, putting her hands flat against the wall. Her vocabulary at that time consisted of the words "hi" and "go." She smiled when the examiner whistled, cried when touched by the examiner, and resisted being measured and weighed. She grasped tongue blades or reflex hammer with four fingers and threw them away immediately.

At 35 1/2 months of age, no further increase in accomplishments was noted although the serum phenylalanine level had been maintained at 5 to 7 mg/100 ml. She weighed 27 lb 6 1/2 oz, her height was 35 in., her head circumference was 48 cm, and chest circumference was 48 cm. She showed affection to her parents and resentment to the examiner. Her muscular development in her extremities, especially in her legs, had improved. After the phenylalanine-restricted diet was started, all EEG were normal except the one at 35 1/2 months of age when there was a suggestion of some four per second spike and wave complexes in light sleep.

The phenylalanine-restricted diet was discontinued at 35 1/2 months. Four and one-half months later, no evidence of regression was evident. During that time she had learned to feed herself in a poor fashion, and

she would remove and replace pegs in a peg-board.

This child showed improvement while receiving the phenylalanine-restricted diet. At first the improvement was marked; toward the end of the treatment it was slower, and by the time the patient reached three years of age no further relative improvement was evident. No regression had occurred four and one-half months after the restricted diet was discontinued.

C. M. (Case F.[12]) (Born Feb. 13, 1955.) This girl was born at term after a long labor and weighed 7 lb 14 oz. She suffered from intermittent eczema from early infancy, frequently had petechiae around the eyes, and bruised easily from very slight trauma. She was able to sit without support when eight months of age. At the age of 14 months, she started to have frequent seizures daily; these consisted of throwing up the arms, stiffening and jerking for about a second.

At time of first examination in this study, when 15 months old, she could not pull herself up but was able to remain in a standing position while holding on to furniture. When the child was supine and a diaper was placed over her face, she made no attempt to remove it. At that time, no eczema was observed and general physical examination was normal. The extremities had flabby musculature which was less well developed peripherally than proximally. The tendon reflexes in the upper extremities were 2 plus, in the lower extremities 1 plus, and the Babinski sign was negative bilaterally.

Diagnosis of phenylketonuria was made at that time. Her serum phenylalanine level was 61 mg/100 ml. An EEG showed typical continuous hypsarhythmia without periods of normalcy.[12]

Ten days after the phenylalanine-restricted diet was started, the phenylalanine level had decreased to 7 mg/100 ml; the seizures were milder and were restricted to periods immediately following awakening. Three weeks after the initiation of the dietary regimen the seizures had decreased further in frequency and severity and the EEG showed periods of normalcy up to 10 to 15 seconds between seizure discharges.

At the age of 20 months, the child laughed when entertained and showed normal affective response to her relatives and the examiner. She was able to "pat-a-cake" and play like a 15-month-old child; she walked well without support. After she had been on the restricted diet for five months, no more seizures were observed. At 24 months of age, the child's motor functions corresponded to those expected at the age of 21 months, her adaptive behavior and language were on the level of a child 15 to 18 months of age, and her personal and social level on a par with that of a child up to 18 months. Her EEG was normal while she was awake and during sleep.

Her actions and behavior responded to the diet rather promptly; the seizures improved markedly within three weeks but did not stop entirely until she had been on the diet for five months. The rate of improvement is less at the present time than during the first few months after treatment was initiated.

W. S. (Born March 15, 1953.) This boy was the second child of a second marriage, his full sibling and three half-siblings being normal. He first sat at nine months and walked unassisted at 19 months of age. His mother's chief complaints were that he engaged in fighting and screaming without provocation. He scratched objects, banged his head against the wall or furniture, and could not be let out of the house alone because he would run into the street and try to touch moving cars. He would defecate all over the house but not in his bed.

On initial examination, age 42½ months, he weighed 32 lb 13 oz, his head measured 49 cm, and the chest 55 cm in circumference. His hair was blond, his eyes dark brown, and there was no history or evidence of eczema. There were no abnormal findings on general physical examination. His deep tendon reflexes were 2 plus to 3 plus and symmetrical, and the Babinski sign was bilaterally negative. The EEG showed a few occipital and generalized spikes while awake and during sleep; there was a negative seizure history. His fasting serum phenylalanine level was 43 mg/100 ml.

A phenylalanine-restricted regimen was started at age 43 months. After two weeks the serum phenylalanine level had decreased to 4 mg/100 ml. The mother reported the following changes: He now showed appropriate fear of moving cars, sought his mother's company, and for the first time showed an affective response to her.

At the time of his fourth birthday, his hair had become noticeably darker, his disposition had improved, and he displayed many activities typical of a three-year-old child.

An EEG at this time showed no evidence of abnormality while the patient was awake or during sleep. The dietary regimen was continued.

M. Y.* (Born Nov. 15, 1953.) This boy was born at term of an uneventful pregnancy. He appeared to be completely normal when examined at three weeks of age. Because he had an older brother with diagnosed phenylketonuria, his urine was tested with ferric chloride at this time for the presence of phenylpyruvic acid, with negative results. At the age of eight weeks he developed a persistent eczema. When the patient was 17 weeks old the ferric chloride test was repeated and this time was positive. At the age of 18 weeks, his fasting serum phenylalanine level was 99 mg/100 ml. At this time he reached and grasped and seemed to have developed normally, but was noted to startle and cry easily, and to sleep restlessly. Height 24½ in.; weight 13 lb 13 oz; head circumference 39.5 cm. A phenylalanine-restricted regimen was started at 19 weeks. Although the infant had seemed to be normal, the mother reported that shortly after commencing the diet he seemed to be calmer and slept better. He has continued to follow a normal pattern of development

* The two patients, **M. Y.** and **S. R.**, were cared for by Dr. P. R. Vandeman, Memorial Clinic, Olympia, Washington, and the recorded observations are his.

on the phenylalanine-restricted diet; at 21 weeks of age he attempted to roll over, when seven and one-half months old he sat alone and played, and at 11 months crawled, pulled up, and cruised, at 14½ months he walked alone and began to say "bye-bye" and "daddy." He had gained in height to 31 in. in weight to 26 lb, and in head circumference to 46 cm. His anterior fontanel closed at seven months, yet head continued to grow normally. He successfully withstood several infectious illnesses during this period. This child differed from the pattern usually shown by phenylketonuric infants in requiring a considerably higher intake of natural protein in order to maintain an adequate serum phenylalanine level (4 to 8 mg/100 ml). On 5 g natural protein per day (estimated 250 mg phenylalanine, corresponding to 25 mg phenylalanine per kg body weight), he consistently had less than 1 mg/100 ml of serum phenylalanine. His daily allowance of natural protein was doubled (50 mg phenylalanine per kg body weight per day) and he then maintained four to eight mg/100 ml serum phenylalanine.

S. R.* (Born Nov. 19, 1956.) This child was born at term of an uneventful pregnancy. He seemed to be normal during the postnatal period and was seen at the age of three weeks for the complaint of a severe eczema. A positive phenylpyruvic acid test was obtained with his urine, and a fasting serum phenylalanine determination at four weeks showed 83 mg/100 ml. A phenylalanine-deficient regimen was commenced at this time. He continued to develop normally. At the age of three months he was alert and responsive, and at five months he smiled, was alert and happy, and could roll over both ways. From the age of 1 month to five months he gained in height from 21¼ in. to 25¼ in., in weight from 8 lb 12 oz to 14 lb 11 oz, and in head circumference from 37 cm to 42 cm.

DISCUSSION

The observations presented here and by other laboratories confirm the previous suggestion that some of the pathologic symptoms in phenylketonuria occur as the result of a deleterious effect of some substance present in phenylketonuria.[3] In addition, further inferences concerning the manner of development of the mental and neurologic impairments may now be made

A new aspect of interest regarding the disorder arises from the finding that many patients with phenylketonuria appear to be normal at birth and during the neonatal period. They then develop pathologic signs, in the form of sudden onset of seizures or signs of retardation, and undergo deterioration. The deterioration appears to involve all demonstrated functions including orientation, affect, and motor abilities; it is coincident with frequent infantile spasms. This impairment of previous ability was first suspected as a result of examination of the application forms of some of the phenylketonuric patients admitted to the Utah State Training School; it was reported that these patients had performed better at an early age than when examined at the institution in the course of these studies. History taken from parents of other phenylketonuric children confirmed this impression.

By now several phenylketonuric infants who have been subjected to expert appraisal have been found to exhibit no signs of neurologic abnormality or retardation. This is true of J. Du, M. Y., and S. R. of the cases described herein, Cases III and VI (the newborn infant described previously)[14] of Horner *et al.*,[8] and the case of Berendes.[6] In addition, the observations stated herein indicate that F. D., A. Du, R. Du, and D. W. probably progressed more rapidly for the first few months of life than later. The fact that children with phenylketonuria are normal at birth and appear to develop normally for a period after birth offers additional encouragement for the hope that a dietary regimen may provide an adequate therapeutic procedure for averting the mental retardation, since a normal, rather than an already damaged, nervous system would be present.

A possible explanation for delay in the development of pathologic symptoms in phenylketonuria has been afforded by the finding that there may be delay in the development of full biochemical abnormalities. This had been anticipated by Delay *et al.*,[15] who reported that an infant whose urine showed only a doubtful positive test for phenylpyruvic acid at two months of age later developed typical phenylketonuria; and by Case 3 of Horner and Streamer[5] whose urine did not contain phenylpyruvic acid during the newborn period, by M. Y., in this paper, whose urine contained no phenylpyruvic acid at three weeks, by Case 6 of Blainey and Gulliford[7] whose urine did not contain phenylpyruvic acid at two weeks of age, and by the newborn infant studied in detail,[14] who did not excrete a detectable amount of phenylpyruvic acid until 34 days of

age. These findings suggest that phenylpyruvic acid is metabolically more closely related to the damaging agent than is phenylalanine.

The suggestion that there are individual variations in the time phenylpyruvic acid first appears in the urine of phenylketonuric infants[14] has been substantiated by observations on another newborn infant with phenylketonuria studied in collaboration with Drs. W. B. Weil, Jr., W. M. Wallace, and J. E. McClelland, University Hospitals of Cleveland, Ohio. This second infant first excreted a barely detectable amount of phenylpyruvic acid at the age of six days, and a readily detectable amount at seven days of age.*

The results now available on the therapeutic effect of phenylalanine restriction in phenylketonuria indicate that children younger than two to three years of age may be remarkably benefited by this type of treatment. The infants reported here who were started on a phenylalanine-restricted regimen before any signs of patholigic changes developed, or immediately after the first signs of abnormality, seem to be developing normally or nearly so. Thus, R. Du is only slightly behind normal, and M. Y. and S. R. show no signs of retardation. Cases III and VI reported by Horner *et al.*[8] and the infant described by Berendes,[6] all of whom were started on the restricted diet at a very early age, seem to be developing normally. The older infants reported here, C. M. and D. W., progressed more rapidly for a time after initiation of the diet than later. M. J., on the other hand, had severe seizures for several months before the restricted diet was initiated, and, although she seemed to have been benefited, remained very retarded.

The effect of dietary treatment of patients older than two to three years of age has been difficult to evaluate. The observations made here and drawn from other reports, however, may be interpreted as indicating that the improvement which is occasionally seen occurs secondarily to the relief of neurologic abnormalities as manifested by seizure disability, which is frequently present. Of the 12 patients described here, five had passed their second birthday when the dietary regimen was commenced. All five of these showed some initial signs of improvement. Four of these patients had seizure disorders, as manifested by abnormal EEG, with or without overt signs of seizures. The EEG of two of these four (S. L. and N. P.) were not markedly improved by the restricted diet; little sustained change in their behavior was observed. The EEG improved and seizures disappeared in the other two (A. Du and W. S.). The regimen was continued only three months with A. Du; with W. S., however, after five months considerable improvement in behavior could be observed.

Other groups have reported improvement, ranging from slight to extensive, in the mentality of older children maintained on restricted diet. Woolf *et al.*[2] described two 32-month-old children and one five and one-half year old child. After the age of 10 months one of the younger children improved from I. Q. 20 to 30; a markedly abnormal EEG at the beginning of the experimental period became essentially normal after 3 months and remained so. The other of the younger children had improved from I. Q. 42 to 49, a less significant change, after ten months; her EEG was considered essentially normal at the beginning of the dietary test. The oldest child did not improve greatly, but it was not reported whether the seizure disorder which was present was greatly benefited by the dietary regimen. Bickel *et al.*[4] reported changes in the mental development of one two-year-old and three older children, without details. Horner and Streamer and collaborators[5,8] reported results with two four-year-old children who demonstrated remarkable improvement as assessed by psychological testing. A boy increased from an I. Q. of 35 at 49 months to 69 at six years; there was no comment concerning his EEG. A girl improved in I. Q. from 37 at four and one-half years to 70 at six years of age; a seizure dis-

* Added in proof. Another newborn infant with phenylketonuria, studied in collaboration with Drs. F. A. Horner and C. W. Streamer, University of Colorado Medical Center, Denver, first excreted a barely detectable amount of phenylpyruvic acid at the age of seven days, and a readily detectable amount at nine days of age.

order present at the beginning of the dietary regimen apparently was improved after only one month. Blainey and Gulliford[7] described their experiences with six older children; these children were followed closely with psychometric testing. Only one of their patients showed significantly increased mental ability as revealed by the testing. It is of interest that their series of patients contained the first case reported by Bickel *et al.*,[1] in whom striking improvement was reported to have occurred by the use of a phenylalanine-restricted diet. Despite the improvement the child was said to have made at that time, the results of the psychometric testing reported by Blainey and Gulliford showed that she had remained at a very low level.

Thus, in nearly all of the cases in whom apparent marked improvement in mental functioning has been observed, there has been an accompanying improvement in seizure disability. Convincing evidence of better mental performance in older patients receiving phenylalanine-restricted diets will have to take into account not only progress occurring as the result of improvement of seizure disorders, but that following increased attention and better acceptance by parents. A further difficulty in clinical evaluation of diet effects lies in the spontaneous improvement which might occur coincidentally with, but not because of, a dietary treatment. The improvement shown by Patient J. Du *off* the diet provides an excellent example that this possibility *can* occur.

The presence in phenylketonuria of some substance with a deleterious effect on the nervous system was well demonstrated by the observations reported here. When the blood phenylalanine level is decreased to the near normal range, the secondary biochemical abnormalities present in phenylketonuria are corrected. In all the patients studied there were marked, though not objectively measurable, changes which accompanied the initiation of the phenylalanine-restricted regimen. Among these were the improved attention span, calmer behavior, and improvement in neurological signs and, usually, improvement in EEG, when abnormal to begin with. Woolf *et al.*[2] described the changes of this sort in one of their patients by stating, "He gave the impression that he had 'become a human being.' " The pathologic signs accompanying high blood phenylalanine levels also were well demonstrated by the behavior of R. Du during the two weeks phenylalanine was returned to his diet, and by the behavior of M. J. during the period she was given phenylalanine. It has been noteworthy, however, in all the patients who have been maintained on restricted diets and then again given natural diets that there has not been a sudden, but a very gradual, return of these signs.

Previous studies, carried out with older patients, failed to show any correlation between biochemical abnormalities and the degree of mental impairment. The recent opportunity for dietary treatment of phenylketonuria has stimulated detection and observations on infants much younger than any included in the earlier reports. As a result of the current studies, the suggestion may be made that two factors influence the mental level of older patients with phenylketonuria. The first is the amount of permanent damage the central nervous system has suffered. This damage occurs in the first two or three years of life either because of an accentuation of the biochemical abnormalities at this age, a greater susceptibility of the rapidly developing nervous system to damaging agents, or a combination of the two. The extent of the damage is dependent upon the age at onset of pathologic signs, and the degree of the biochemical abnormalities. The second factor influencing the observed status of older patients is the continuing presence of some neurotoxic agent(s). The rapid initial improvement observed in patients given a phenylalanine-restricted diet would be regarded as occurring as a result of the removal of the toxic agent(s). This would allow the brain to function at a level conditioned by the extent of the damage previously suffered during the first two or three years. The probability that the extent of early damage influences the effect of the deleterious metabolites is indicated by the fact that older, untreated phenylketonurics, with typical biochemical abnormalities, can be mentally normal.[16]

The presence of an upper age limit of two to three years after which no further damage occurs is suggested by (1) the previous observation that further mental deterioration is not usually observed in older patients,[17] and (2) by the absence of consistent improvement in older patients, in conjunction with the improvement observed in children less than two years old under the influence of a phenylalanine-restricted diet. The likelihood that there is this upper age limit after which severe damage to the nervous system no longer occurs is of considerable practical importance. Since phenylketonuria in older children is not incompatible with normal or near normal intelligence,[16] it might not be necessary to continue feeding phenylketonuric children the synthetic diet, with its attendant nutritional difficulties, after they attain this age. As a corollary, it would follow that it would be of little advantage to try to maintain older patients on the dietary regimen unless they have seizures or are extremely hyperactive.

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REFERENCES

1. Bickel, H., Gerrard, J., and Hickmans, E. M.: The influence of phenylalanine intake on the chemistry and behavior of a phenylketonuric child. *Acta Pediat.* 43: 64, 1954.
2. Woolf, L. I., Griffiths, R., and Moncrieff, A.: Treatment of phenylketonuria with a diet low in phenylalanine. *Brit. Med. J.* 1: 57, 1955.
3. Armstrong, M. D., and Tyler, F. H.: Studies on phenylketonuria. I. Restricted phenylalanine intake in phenylketonuria. *J. Clin. Investigation* 34: 565, 1955.
4. Bickel, H., Boscott. R. J., and Gerrard, J.: Observations on the Biochemical Error in Phenylketonuria and Its Dietary Control in *Biochemistry of the Developing Nervous System*, Academic Press, New York, 1955, p. 417.
5. Horner, F. A., and Streamer, C. W.: Effect of a phenylalanine-restricted diet on patients with phenylketonuria. *J. A. M. A.* 161: 1628, 1956.
6. Berendes, H.: Prevention of mental retardation in phenylpyruvic oligophrenia by early dietary treatment. Presented at Fourth Annual Meeting, Western Soc. Pediat. Res., 1956.
7. Blainey, J. D., and Gulliford, R.: Phenylalanine-restricted diet in the treatment of phenylketonuria. *Arch. Dis. Childhood* 31: 452, 1956.
8. Horner, F. A., Streamer, C. W., Clader, D., Hassel, L. L., Binkley, E. L., Jr., and DuMars, K. W., Jr.: Effect of a phenylalanine-restricted diet on patients with phenylketonuria II. *A.M.A. Am. J. Dis. Child.* 93: 615, 1957.
9. Armstrong, M. D., and Low, N. L.: Studies on phenylketonuria. VIII. Relation between age, serum phenylalanine level, and phenylpyruvic acid excretion. *Proc. Soc. Exp. Biol. Med.* 94: 142, 1957.
10. Gibbs, E. L., Fleming, M. M., and Gibbs, F. A.: Diagnosis and prognosis of hypsarhythmia and infantile spasms. *Pediatrics* 13: 66, 1954.
11. Ford, F. R.: *Diseases of the Nervous System in Infancy, Childhood, and Adolescence*, ed. 3, Thomas, Springfield, 1952, p. 273.
12. Low, N. L., Bosma, J. F., and Armstrong, M. D.: Studies on phenylketonuria VI. EEG studies in phenylketonuria. *A.M.A. Arch. Neurol. Psychiat.* 77: 359, 1957.
13. Armstrong, M. D., Shaw, K. N. F., and Robinson, K. S.: Studies on phenylketonuria II. The excretion of *o*-hydroxyphenylacetic acid in phenylketonuria. *J. Biol. Chem.* 213: 797, 1955.
14. Armstrong, M. D., and Binkley, E. L., Jr.: Studies on phenylketonuria V. Observations on a newborn infant with phenylketonuria. *Proc. Soc. Exp. Biol. Med.* 93: 418, 1956.

15. DELAY, J., PICHOT, P., DELBARRE, F., and TASEEL, J.: L'oligophrénie phénylpyruvique. Nouvelles observations. *Bull. et Mem. Soc. Med. Hôp. Paris* 64: 669, 1948.

16. LOW, N. L., ARMSTRONG, M. D., and CARLISLE, J. W.: Phenylketonuria. Two unusual cases. *Lancet* 2: 917, 1956.

17. JERVIS, G. A.: Phenylpyruvic oligophrenia; introductory study of fifty cases of mental deficiency associated with excretion of phenylpyruvic acid. *A.M.A. Arch. Neurol. Psychiat.* 38: 944, 1937.

Dietary Prescription of Water, Sodium, Potassium, Calcium and Phosphorus for Infants and Children

By EDWARD L. PRATT, M.D.*

PHYSICIANS prescribing diets for children must recognize the two distinctive functions of foodstuffs.[1] The first is to supply those substances that sustain the structural machinery of the body. The second is to furnish energy for this machinery. The specific units of the mobile and the stationary chemical structure cannot be provided by substituting large amounts of other substances. When used for energy foodstuffs are widely interchangeable.

The danger in considering specific nutrients is that by so doing we may displace our emphasis which must always be upon foods with their unknown as well as known contributions. Our patients will not benefit from our knowledge of nutrition except as we talk to them in terms of household measures of common foodstuffs. Specific prescriptions must be used as to the types and amounts of food and not vague statements about eating "a well balanced diet".[2]

The advantage of considering specific nutrients is that by so doing we see more clearly the interrelationships of foods and the need for a variety of natural foods. We are also more aware of the areas where additional research is required. Such considerations point out how unsound and inadequate it is to resort to multiple concentrates of "known" nutrients in attempting to provide good nutrition.

From the Department of Pediatrics, University of Texas Southwestern Medical School, Children's Medical Center and Parkland Memorial Hospital, Dallas, Texas.

* Professor and Chairman of the Department of Pediatrics of the University of Texas, Southwestern Medical School, Dallas, Texas.

Some of the indispensable structural elements are stored in fair quantity against intervals of deprivation, whereas no appreciable stores exist for others, such as water, sodium and potassium. For each of these intake must continuously balance outgo. The physician, to provide their intake without causing insufficiency or excess, needs to consider their outgo and the range over which outgo may wander in health.

WATER

The prescription of water intake for healthy children presents no problem once the child can express his thirst in a meaningful way so that he is given water or can get it for himself whenever he is thirsty. Prior to reaching this stage of development, the water intake must be prescribed. To do this requires an understanding of water expenditure in health.[3]

The insensible losses of water from the lungs and skin amount to 42 ml of water per 100 cal metabolized, which, *for the infant*, is conveniently approximately equivalent to the same figure per kilogram of body weight. The water required for urine formation is proportional to the load of substances, chiefly urea and electrolytes to be excreted by the kidneys, and is inversely proportional to the concentration of the urine.[4] Table I illustrates the effect of the type of diet and the concentration of the urine on the range of urine volumes. Water lost in the stools is negligible and that required for growth (about 70 ml per 100 g gained) is also of minor importance in calculating daily water expenditure. Although sweat is generally considered an abnormal loss, there is evidence that infants, children and

TABLE I

Urine Volumes Required by Different Diets
(Urine Volumes in ml/kg/day)

Type of diet	Approx. renal osmolar load mosm/kg	Concentration of urine		
		Dilute	Isotonic	Maximally concentrated
Low-protein low-mineral (human milk)	14	190	45	12
Average (diluted cow's milk with added carbohydrate)	21	250	67	17
High protein high mineral	45	560	145	40

adults in comfortable environmental temperatures usually produce about 10 g of perspiration per 100 cal metabolized.[3] Therefore, for the healthy infant, water intake and the water of oxidation (about 12 ml per kg) together should furnish each day around 50 ml per kg of body weight for insensible losses plus slight sweating, 70 ml per kg for urine formation for the artificially fed infant (45 ml for breast fed) and an additional 25 to 50 ml per kg as a margin of safety, especially against increased perspiring. An appreciation of these physiologic principles allows the physician to anticipate the effects of prescribing more dilute or concentrated feeding mixtures or those high in protein or electrolytes. Thus the use of more dilute cow's milk mixtures for the first week of life is advocated because they impose a lighter renal load at a time when renal concentrating power is low. Similarly, the rationale of the "routine" use of cow's milk mixtures having 20 per oz (670 cal/lit for young infants can be appreciated, since the water requirement will automatically be met if the caloric intake is adequate. For the older infant, liquids in addition to his milk may be furnished to maintain his water intake at a proper level.

SODIUM AND POTASSIUM

In health, the amounts of sodium and potassium in the body are regulated primarily by the dietary intake and the renal output of these ions. They are almost completely absorbed from the gastrointestinal tract, and amounts absorbed in excess of the body's needs for growth are promptly excreted in the urine. The allowances for sodium and potassium, like other structural chemical units, are best viewed in terms of minimal requirements and the maximal amounts that can be physiologically tolerated. The minimal amounts of these two minerals depend largely on the quantities needed for growth, for the usual sweating, and on their conservation by the kidneys.

The requirements for growth are difficult to estimate. The "precise misinformation"[1] of balance studies has confused this subject. Extrapolation of the "retentions for growth," especially those for infants fed cow's milk compared with those fed human milk, could only lead to widely varying composition of the body fluids. Yet whole body analyses and isotope dilution studies indicate a quite constant composition of this portion of the body (except for its fat content). The composition of bone may be less constant, and the content of calcium and phosphorus in bones may vary with intake. The best estimates for growth in young infants are, for each kilogram of body weight gained, around 76 meq of sodium, 58 meq of chloride and 46 meq of potassium,[5] although these values may be 5 to 10 per cent too high judging from the isotope dilution studies.

Under comfortable environmental conditions a small amount of perspiration is formed. Recent data indicate that the losses of sodium and potassium were originally estimated too high and that more realistic figures are of the order of 0.1 to 0.2 meq of sodium and chloride as well as for potassium per 100 cal metabolized during infancy.[6]

The urine, except in the neonatal period, may be rendered nearly free of electrolytes so that minimal urinary losses are approximately 0.2 meq of sodium and chloride and 0.4 meq of potassium per 100 cal metabolized.[3] Stool losses are around 0.2 meq of each of these electrolytes per 100 cal metabolized.

For practical purposes, the lowest usual daily intakes of sodium and potassium for

young infants are those supplied by human milk. An infant ingesting 165 ml of human milk per kg of body weight per day ($2^1/_2$ oz/lb) would receive about 1 meq of sodium (23 mg), 2 of potassium (78 mg) and 1.7 of chloride (60 mg) per kg of body weight.[7]

The maximal intakes of sodium and potassium that can be tolerated have not been defined. High intakes of sodium have an adverse effect on potassium balance and vice versa,[8] and high electrolyte intakes demand a large supply of water for urine formation. A practical upper limit of daily sodium and potassium intake in infancy may be taken as the amounts ingested by an infant taking 110 cal per kg of body weight per day of skimmed cow's milk. Under these circumstances the intake of sodium and potassium would be about 8.0 (185 mg) and 11.0 (430 mg) meq/kg/day respectively.

For older children, low-sodium diets containing as little as 2.5 meq (58 mg) of sodium daily have been used.[9] Probably much above 260 meq of sodium (6 g of sodium; 15 g of NaCl) per day are not well tolerated. Data for minimal and maximal daily amounts of potassium for children and adolescents are unknown, but probably are in the range of 40 meq (1.6 g) to 250 meq (10 g) per day (10). Ordinary diets for 12-year-old children provide about 90 meq of potassium daily and additions of 150 meq per day have been used without harmful effects.[9]

Therefore, the conclusion is that suitable amounts of sodium and potassium are provided by simple milk diets in infancy and by all well balanced diets for children. Potassium is not apt to be present in either too small or too large amounts. Sodium in ordinary good diets is generally ample for all conditions, except possibly strenuous exercise by older children is hot humid environments. Added salt is not needed nor helpful in the diets of healthy infants in hot weather. Excessive sodium intake may occasionally occur because too much salt is added to foods during preparation or at the table.

CALCIUM AND PHOSPHORUS

Assessing the needs for calcium and phosphorus is difficult because the large stores provide for long periods of depletion or repletion without leading to recognizable changes in well being, thus making for much speculation as to the significance of the balances which have been obtained under varying conditions of intake, age and states of health. Analyses of the amounts of calcium and phosphorus in bodies at varying ages could provide data to calculate requirements, but the variability of the few analyses available and particularly the suspicion that the subjects were not in good nutritional condition invalidate such calculations.[10] Are we justified in concluding that because increased intakes of calories, protein and calcium produce taller, heavier framed adults, these intakes are better nutritionally; or that such diets used in early life will lessen the incidence of bone disorders in the adults, or alter the extent of cardiovascular degenerative diseases? Henry and Kon[11] found that growing rats given low-calcium diets deposited it more slowly than those on higher intakes, although eventually bone analyses showed similar calcium content for all rats. However, senescent rats accustomed to do with little calcium in the diet remain in calcium equilibrium in circumstances leading to calcium loss in rats used to a higher intake. Thus it appears that the way calcium stores are accumulated may determine the plane of calcium metabolism. Either the slowly acquired stores are more tenaciously held or those rats have developed a more efficient turnover of calcium. If humans could be shown to behave in a similar manner, calcium intakes lower than those generally advocated might be desirable for children.

Phosphorus intake will be ample in diets with adequate amounts of protein and calcium. Hence, this discussion will deal chiefly with calcium, although it is evident from Figure 1 that the status of calcium in the body fluids depends not only on the flow of calcium into and out of the body fluids but also upon the rates of entrance and exist of phosphorus. The phosphorus concentration in the circulating fluids is determined by the rate of absorption from the gastrointestinal tract and the equilibrium with the intracellular and skeletal

phosphates as well as alterations in renal excretion.[12] A resume of the factors influencing calcium and phosphorus metabolism is given in Figure 1.[13,14] Thus it is obvious that the requirement of these minerals may vary widely, and that minimal and maximal amounts tolerated in the diet cannot be readily defined under most circumstances. Data on the quantities of *endogenous* calcium excreted in the feces at different ages, as well as on the factors influencing this route of excretion, would help

load incurred by cow's milk feedings,[17,18] the low glomerular filtration rate of this period[19,20] and the influence of stress, both in releasing phosphorus from body tissues and in reducing glomerular filtration.[21] Temporary parathyroid hypofunction probably plays a role,[22] although lack of agreement[20,23] as to what objective evidence indicates parathyroid activity leaves its role uncertain. Figure 1 demonstrates that the observed values of serum calcium and phosphorus in neonatal hypocal-

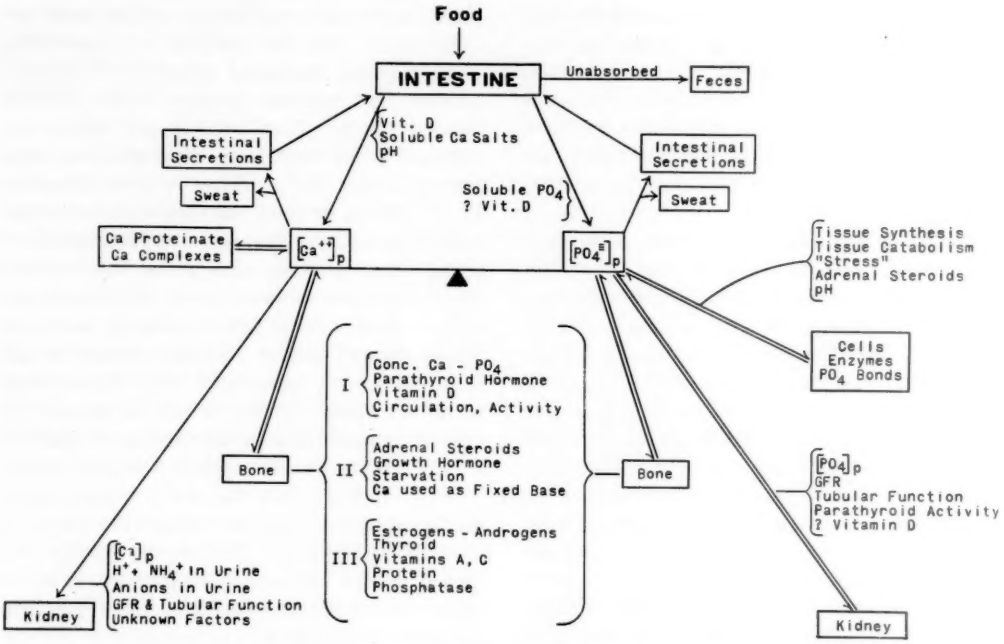

Fig. 1. Factors influencing calcium and phosphorus metabolism[12,13]. Those affecting bone are subdivided: I are those quite well understood, II those about which something is known, and III those dimly discerned.

in defining the utilization of dietary calcium.[15] Perhaps the great variability of the human organism in its disposal of dietary calcium and particularly the marked ability of the body to adapt itself to a wide range of calcium intakes are the major factors leading to our uncertainty as to the requirement of this mineral.[16]

In the neonatal period, hypocalcemia is occasionally noted. An extensive literature attempting to explain the causes for these cases stresses the factors of the high phosphate

cemia could be brought about by any or all of these factors, and not necessarily by diet alone.[24]

In artificially fed infants the use of a special modification during the neonatal period is generally prescribed for the reasons discussed under water requirement and in this section, although there is not unanimous agreement as to the need for such mixtures. A commonly employed mixture during the first week of life is: cow's milk 1 part, water 2 parts, added carbohydrate 5 to 10 g per 100 ml, with or

without the addition of 0.28 g of calcium gluconate per 100 ml.[17]

Beyond the first week of life, artificially fed infants on cow's milk modifications providing 120 mg of calcium per kg per day are generally believed to have an adequate calcium intake if 400 to 800 units per day of vitamin D are taken. This amount of calcium is furnished by cow's milk modifications in which $^2/_3$ or $^7/_{10}$ of the calories come from cow's milk and the other $^1/_3$ or $^3/_{10}$ of the calories from added carbohydrate. There is evidence that calcium intakes of 50 mg/kg/day with adequate amounts of vitamin D are about the minimal calcium intake for infants fed *cow's* milk mixture.[10]

For healthy, full term infants the relatively small amounts of calcium ingested from human milk, around 40 to 60 mg/kg of body weight per day, seem adequate if about 400 units of vitamin D per day are taken. The absorption of calcium from human milk ranges from 50 to 70 per cent.

From infancy to around 8 years of age the generally accepted daily intake of calcium ranges from 70 mg/kg of body weight for the three-year-old child to 45 mg/kg of body weight for the eight-year-old child. Three cups of milk per day or one pint of milk plus a daily serving of cheese, or ice cream or custard, along with the vegetables, cereals and bread needed to furnish other nutrients will supply these amounts. Plenty of exposure to sunshine or an intake of 400 units of vitamin D each day appear to be appropriate. In order to encourage eating of wide variety of foods it is frequently desirable to restrict the intake of milk to these amounts in the second and third years. Diagrams which are helpful in illustrating the interrelationships of all food items have been given by Butler[25] for preschool children and by Boyd[26] for school children.

The preschool period is one of decreased rate of skeletal growth, of an increased percentage of the body weight in muscle, and of small food intake along with frequent infections. To develop good eating habits during this period one needs to prescribe a variety of foodstuffs high in nutrient values and, usually, to prohibit too much of a single high caloric food.

In the early school years the daily quota of milk should be one quart or its equivalent in the substitutes mentioned above. Minimal daily intakes of calcium have been estimated at around 35 and 25 mg/kg of body weight per day at three and eight years of age respectively.[10]

Higher intakes of calcium and vitamin D during the age period eight to twenty years are being advocated.[13] Calcium intakes of 1.4 to 1.7 g per day accompanied by at least 1,000 units of vitamin D are suggested.[27] A quart and a half of milk each day or substitutes of dairy products are needed to supply this amount of calcium. These estimates of needs are based largely on balance data and exceed the dietary calcium intake of children of similar age in many parts of the world.

TABLE II

Current Estimates of Desirable Intakes of Calcium and Vitamin D

Age group	Estimated need for calcium	Foods (for higher estimated need)	Estimated need for vitamin D
Infancy			
Breast fed	40 mg/kg/day	Human milk	400 u. vit. D.
Artificial feedings	70–120 mg/kg/day	$^2/_3$ of calories from cow's milk	400 u. vit. D.
Preschool	0.5–0.8 g/day	3 cups of milk or equivalents of cheese, ice cream, custards, plus vegetables, cereals, bread	None to 400 u. vit. D.
6–8 years	0.7–1.0 g/day	1 quart of milk or equivalents plus vegetables, cereals, bread	?added vit. D.
Peri-puberty 9–18 years	1.0–1.5 g/day*	$1^1/_2$ quarts of milk or equivalents plus vegetables, cereals, bread	?800–?3,000 u. vit. D.

* Possibly larger than necessary (see text).

The evidence that these smaller intakes are detrimental is not substantial. Thus it may be that the amounts of calcium traditionally recommended in this country are unnecessarily generous. More data is clearly required in this age period.

The period preceeding, during and following puberty is apparently one of nutritional stress; one of wide fluctuations in protein and mineral balances, without much understanding of the causes or their significance. Minimal requirements have been placed as low as 7 mg/kg of body weight per day for young adults.[10] Excessive intakes or intestinal absorption of calcium are seldom encountered except where milk and cream diets with alkalis are prescribed[13] or larger than usual amounts of vitamin D are ingested, especially by infants unusually sensitive to vitamin D.[28]

The current estimates of calcium intakes for good health are summarized in Table II.

REFERENCES

1. GAMBLE, J. L.: The general terms of the food requirement, in BRENNEMAN, J.: *Practice of Pediatrics*, Vol. 1, W. F. Prior, Hagerstown, Md., 1957, Chap. 23, p. 1–10.
2. *Nutrition for Every Day Use.* Nat. Dairy Council, Chicago, 1954.
3. DARROW, D. C., and PRATT, E. L.: Fluid therapy, relation to tissue composition and the expenditure of water and electrolyte. *J.A.M.A.* 143: 365; 143: 432, 1950.
4. GAMBLE, J. L., and BUTLER, A.: Measurement of renal water requirement. *Tr. A. Am. Phys.* 58: 157, 1944.
5. GAMBLE, J. L., WALLACE, W. M., ELIEL, L., HOLLIDAY, M. A., CUSHMAN, M., APPLETON, J., SHENBERG, A., and PIOTTI, J.: Effects of large loads of electrolytes. *Pediatrics* 7: 305, 1951.
6. COOKE, R. E., PRATT, E. L., and DARROW, D. C.: The metabolic response of infants to heat stress. *Yale J. Biol. & Med.* 22: 227, 1950.
7. *The Composition of Milks*, Revised 1953. Pub. 254, Nat. Res. Council, Washington, D. C., 1953.
8. GAMBLE, J. L.: *Companionship of Water and Electrolytes in Organization of Body Fluids.* Lane Medical Lectures, Stanford Univ. Press, Stanford, 1951.
9. GREENMAN, L., WEIGAND, F. A., MATEER, F. M., and DANOWSKI, T. S.: Cortisone therapy of initial attacks of rheumatic carditis. *A.M.A. J. Dis. Child.* 89: 426, 1955.
10. SHOHL, A. T.: Mineral Metabolism. *Monog. Am. Chem. Soc.*, New York, Rheinhold, 1939.
11. HENRY, K. M., and KON, S. K.: The relationship between calcium retention and body stores of calcium in the rat: Effect of age and of vitamin D. *Brit. J. Nutrition* 7: 147, 1953.
12. SMITH, H. W.: *The Kidney: Structure and Function in Health and Disease.* Oxford University Press, New York, 1951.
13. STEARNS, G.: Human requirement of Calcium, Phosphorus and Magnesium, in *Handbook of Nutrition*, ed. 2, A.M.A., Chicago, 1951.
14. Combined Staff Clinic: Bone and metabolic diseases of bone. *Am. J. Med.* 15: 99, 1953.
15. BLAU, M. SPENCER, H., SWERNOZ, J., GREENBERG, J., and LASZLO, D.: Effect of intake level on the utilization and intestinal excretion of calcium in man. *J. Nutrition* 61: 507, 1957.
16. STEGGERDA, F. R., and MITCHELL, H. H.: Variability in the calcium metabolism and calcium requirements of adult human subjects. *J. Nutrition* 31: 407, 1946.
17. GARDNER, L. I., MACLACHLAN, E. A., PICK, W., TERRY, M. L., and BUTLER, A. M.: Etiologic factors in tetany of newly born infants. *Pediatrics* 5: 228, 1950.
18. GITTLEMAN, I. F., and PINCUS, J. B.: Influence of diet on occurrence of hyperphosphatemia and hypocalcemia. *Pediatrics* 8: 778, 1951.
19. SNELLING, C. E.: Disturbed kidney function in the newborn infant associated with decreased calcium: Phosphorus ratio. *J. Pediat.* 22: 559, 1943.
20. MCCRORY, W. W., FORMAN, C. N., MCNAMARA, H, and BARNETT, H. L.: Renal excretion of inorganic phosphate in newborn infants. *J. Clin. Investigation* 31: 357, 1952.
21. MCCANCE, R. A., and WIDDOWSON, E. M.: The influence of events during the last few days in utero on tissue destruction and renal function in the first two days of independent life. *Arch. Dis. Childhood* 29: 495, 1954.
22. BAKWIN, H.: Pathogenesis of tetany of the newborn. *Am. J. Dis. Child.* 54: 1211, 1937.
23. CRAWFORD, J. D., OSBORNE, N. M., TALBOT, N. B., TERRY, M. L., and MERRILL, M. P.: The parathyroid glands and phosphorus homeostasis. *J. Clin. Investigation* 29: 1448, 1950.
24. GRAHAM, G. G., BARNESS, L. A., and GYÖRGY, P.: Serum calcium and inorganic phosphate in the newborn infant, and their relation to different feedings. *J. Pediat.* 42: 401, 1953.
25. BUTLER, A. M.: Nutritional requirements in infancy and in childhood. *Am. J. Dis. Child.* 64: 898, 1942.
26. BOYD, J. D.: Prescribed diets for normal children. *J. Pediat.* 24: 616, 1944.
27. JOHNSTON, J. A.: Adolescence, in BRENNEMAN, J.: *Practice of Pediatrics*, Vol. 1, W. F. Prior, Hagerstown, Md., 1957, chap. 10, p. 13.
28. DAESCHNER, G. L., and DAESCHNER, C. W.: Severe idiopathic hypercalcemia of infancy. *Pediatrics* 19: 362, 1957.

Abnormally High Pyridoxine Requirement

SUMMARY OF EVIDENCE SUGGESTING RELATION BETWEEN THIS FINDING AND CLINICAL PYRIDOXINE "DEFICIENCY"

By ANDREW D. HUNT, JR., M.D.*

THE EVIDENCE for the existence of a congenitally abnormally high requirement for vitamin B_6 has been slowly accumulating since the first demonstration by Snyderman *et al.*[1] of the effects of deficiency of this vitamin in the human infant.

Beginning in 1951, an outbreak of convulsions in infants, usually less than four months of age, was observed in widely scattered parts of the United States and reported by several authors.[2–5] It was ascertained that the common denominator in these cases was the diet; namely a brand of liquid, infant-feeding mixture which, due to changes in autoclaving procedures, was found to contain in the neighborhood of 60 mcg of vitamin B_6 per reconstituted quart. The syndrome was remarkably uniform, with irritability, "colic," and general unhappiness being followed by severe, often prolonged generalized convulsions. Changing to another formula, or giving vitamin B_6 by mouth or parenterally, promptly stopped the seizures.

Routine study of these infants, in general, revealed essentially normal findings, with the exception of somewhat elevated spinal fluid protein in some cases. The electroencephalogram was normal except during a seizure, and this seizure pattern was shown[4] to revert to normal with remarkable rapidity upon the intramuscular administration of a large dose of pyridoxine.

From the Hunterdon Medical Center, Flemington, New Jersey, and the Department of Pediatrics, New York University College of Medicine.

* Director of Pediatric Services, Hunterdon Medical Center, Flemington, New Jersey, Assistant Professor of Pediatrics, New York University College of Medicine, New York, N. Y.

However, the actual number of infants developing convulsions was a very small percentage of those who were fed the deficient feeding mixture.

This problem has recently been studied by Bessey *et al.*[2,3] who investigated five such infants. One liter per day of an evaporated milk mixture, containing an estimated 0.25 mg of vitamin B_6 was sufficient to prevent further seizures. In one of these infants, intensive biochemical studies were performed, and 1.0 to 1.2 mg of vitamin B_6 was required to prevent xanthurenic acid excretion after a tryptophane load. It seems unfortunate that these authors did not have the opportunity for a similar study of the other infants who convulsed on the pyridoxine-poor mixture, for the findings in this one case suggest an explanation for selection of susceptibility to a nearly adequate intake of vitamin B_6. In the control group of eight infants, xanthurenic acid excretion after a tryptophan load was prevented in all but one case by amounts of pyridoxine ranging from 0.2 to 0.4 mg. In this one exceptional case, considerable xanthurenic acid was excreted in spite of a pyridoxine intake of 0.20 mg. Titration of intake necessary to prevent this finding was not performed, but excretion of xanthurenic acid was eliminated by a single dose of 5 mg of pyridoxine hydrochloride. The authors, however, assume that this baby's vitamin B_6 requirement to prevent xanthurenic acid excretion was above 1 mg daily, as was the case in the convulsing infant who was so tested.

Thus, any statistical difference between the control and experimental groups is lacking, and one can only speculate that the control infant with the apparently high vitamin B_6 re-

quirement would have convulsed if given the pyridoxine-poor feeding, and that a suggestion exists that the infants who suffered convulsions on the deficient commercial milk preparation were actually subjects with a pyridoxine requirement which is higher than usual.

Bessey *et al.* also describe two breast-fed infants with convulsions relieved by a calculated intake of 0.26 mg pyridoxine daily. These two infants also required upwards of 1.0 mg pyridoxine to prevent excretion of xanthurenic acid after a tryptophan load. The breast milk given one of these infants was found to contain but 0.067 mg per quart of pyridoxine.

Thus, the suggestion is again apparent that convulsions may occur in susceptible infants as a result of a borderline intake of vitamin B_6, and that such a barely adequate intake can occasionally at least be a natural phenomenon. It is emphasized by the authors that the amount of vitamin B_6 required to prevent excretion of xanthurenic acid after a tryptophan load is markedly greater than that required to prevent convulsions. It is assumed that two different vitamin B_6 dependent mechanisms are being reflected in the two end points. Thus it is thought that the biochemical evidence for vitamin B_6 deficiency is more sensitive than the clinical manifestation and will appear first in the course of progressive withdrawal of the vitamin. Conversely, with clinical symptoms of pyridoxine deficiency, these manifestations are abolished with a smaller amount of vitamin B_6 than is the excretion of xanthurenic acid after a tryptophan load.

First reported in 1952, and published in 1954[6] was the case of a newborn female infant suffering from intractable convulsions which failed to respond to the usual anticonvulsant measures. All studies were essentially unrevealing except for a markedly increased spinal fluid protein. Eventually, and quite by accident, it was discovered that the intramuscular injection of a multivitamin preparation containing 6 mg pyridoxine abruptly brought an end to the convulsions, and that the duration of effect was slightly upward of 48 hours. Finally, 2 mg of pyridoxine given orally was found to prevent convulsions for approximately 48 hours, and nearly two years later this dose was still apparently necessary to maintain the child in a seizure-free state.

Xanthurenic acid was not excreted after a tryptophan load in this case. It was concluded that this infant did not represent the characteristic picture of vitamin B_6 deficiency, but rather that she was suffering from a metabolic aberration producing an abnormal need for pyridoxine, either as a result of increased destruction of the vitamin, or of some other mechanism. Of interest was the fact that the child's mother had received large amounts of intramuscular vitamin B_6 during the first trimester of pregnancy, because of severe nausea and vomiting. She had had two previous pregnancies. The first, during which there had been no pyridoxine medication, had resulted in the birth of a normal infant. During the second pregnancy, vitamin B_6 had been given during the first three months, and the baby had died in the neonatal period with severe convulsions. It was therefore tempting to relate the pyridoxine "dependency" to the vitamin B_6 medication during pregnancy.

An attempt was made to subject this hypothesis to an experimental test. It is known that suckling rats, with their mothers on a pyridoxine-deficient diet, lose weight, frequently convulse at about three weeks of age, and some die. Pregnant rats were divided into two groups; the experimental group was given massive amounts of pyridoxine mixed in the daily ration during the first half of pregnancy; the control group was given the usual diet. After delivery, both groups were given a diet devoid of vitamin B_6. Had the theory that "dependency" was the result of vitamin B_6 administration during pregnancy been valid, one would have expected a more rapid incidence of convulsions and weight loss in the infant rats born of the mothers who had been fed loading doses of pyridoxine during pregnancy. No such correlation, however, was observed in any of the trials; indeed, if there were any positive results, they were in the opposite direction, with the offspring of the experimental group having a slightly better weight gain than those in the control group.[7] Experimental evidence in support of the hypothesis that abnormal need

for vitamin B_6 could be related to overdose of this substance during pregnancy is therefore lacking.

Bessey *et al.*[3] describe two newborn infants who appear to resemble Hunt's case.[6] They required 5 and 2 mg of vitamin B_6, respectively, to control convulsions, and both needed in the neighborhood of 2 mg per day to prevent convulsions over a period of several months. One of these infants is stated to be developmentally retarded. Neither is reported to have abnormal spinal fluid findings. One of these cases excreted no xanthurenic acid after a tryptophan load; the other excreted a small amount, which was abolished by but 0.4 mg of pyridoxine. This amount is in sharp contrast to the 5 mg required to prevent convulsions. The authors point out that these two infants, presumably representing aberrations of vitamin B_6 metabolism, demonstrate a situation quite the reverse of that seen in the infants whose convulsions were related to a decreased intake of vitamin B_6. In the latter group, it will be remembered, the quantity of pyridoxine required to prevent convulsions was much less than that required to abolish the xanthurenic acid test.

Neither of Bessey's two cases of "pyridoxine dependency" gave a history of maternal medication with vitamin B_6 during pregnancy.

Although anemia was the chief manifestation of one of Snyderman's infants[1] with induced B_6 deficiency, this does not appear to have been a significant part of the clinical picture of the thus far reported infants with symptoms related to vitamin B_6 intake. A recent report by Harris *et al.*[8] describes a case of "pyridoxine responsive anemia" in a 27-year-old man, who was first seen in 1947 with a hypochromic anemia (4.5 g hemoglobin per 100 ml) which was unresponsive to iron, liver extract, yeast, folic acid, and ascorbic acid. One year later, a spontaneous remission ensued which continued until 1953. When severe anemia recurred, pyridoxine hydrochloride, in a dosage of 200 mg intramuscularly daily for five days was accompanied by a reticulocyte response to 50.8 per cent, with a subsequent rise in hemoglobin to 13 g per 100 ml. Within 11 weeks, the hemoglobin had again fallen to 7.8 g per 100 ml. At that point, 1 mg pyridoxine intramuscularly failed to produce a response; however, 10 mg daily for seven days produced a good reticulocyte response and a rapid rise of hemoglobin to 14.1 g per 100 ml. Biochemical investigation of this patient revealed abnormalities of tryptophan metabolism which were partly corrected by 1 mg pyridoxine, and completely rectified by 10 mg.

In the older child and adult, there is evidence that convulsions[9,10] and abnormal electroencephalographic findings[10–13] may rarely be rectified by the administration of vitamin B_6. However, the preponderance of experience indicates that pyridoxine lacks a pharmacologic anticonvulsant action; trials of this substance in various forms of epilepsy have, in general, failed.[14] It would therefore appear probable that the therapeutic effect of administered pyridoxine represents the correction of a deficiency specifically at the level of central nervous system function. As in the case of pyridoxine "dependency" previously discussed, other symptoms and signs of Vitamin B_6 deficiency in the human as described by Vilter[15] were absent in these cases. It is notable furthermore that convulsions are not described by Vilter in adults made Vitamin B_6-deficient through the administration of desoxypyridoxine.

Therefore, the evidence concerning variations in body requirements for vitamin B_6, scattered and incomplete as it is, appears to indicate three general types of situation.

(1) The widespread incidence of seizures in infants fed a commercial milk preparation deficient in vitamin B_6 together with the data of Bessey *et al.* quoted above, appears to indicate moderate variation in pyridoxine requirements in normal infants. Such infants, when given feedings containing a quantity of vitamin B_6, apparently adequate for the majority of the infantile population, are likely to suffer convulsions. Although but a few such infants have been studied from this standpoint, the amount of added pyridoxine required to protect against seizures is small. It is also considerably less than the amount required to reverse the biochemical evidence of deficiency represented by the xanthurenic acid test. It is to be noted

that two of Bessey's cases were breast fed, so that this syndrome may not directly be related to cow's milk.

(2) Congenital abnormalities of metabolism of vitamin B_6, are characterized by severe convulsions in infants, in spite of usually adequate pyridoxine intake. Three such infants seem now to have been reported. The quantity of vitamin B_6 required to prevent seizures in these apparently rare cases is of a much higher order of magnitude than the effective dose in those infants in group 1. Furthermore, there seems to be a basic metabolic difference. In the three reported cases, xanthurenic acid tests were normal. Thus, there was no evidence of a biochemical deficiency even though relatively huge amounts of pyridoxine were required to prevent or stop convulsions. It therefore seems likely, in view of freedom from generalized clinical or biochemical evidence of pyridoxine lack, that these infants are suffering from a metabolic cerebral anomaly characterized by an abnormal need for, or utilization of, vitamin B_6 by the brain.

(3) The third group consists of the few adults who have had symptoms relieved by pyridoxine. Among them are the few patients whose seizures seem to have been relieved by vitamin B_6, and the well documented case of pyridoxine-responsive anemia mentioned above. The latter patient was demonstrated to have biochemical evidence of deficiency, with the identical dose of vitamin B_6 being required to reverse both the xanthurenic acid test and the clinical symptom of anemia. This is, of course, in contrast to the pyridoxine-dependent infants, where there was no demonstrable biochemical deficiency. Perhaps different metabolic systems are involved, and the evidence of pyridoxine deficiency as reflected in failure of hematopoiesis is more closely related to excretion of xanthurenic acid after a tryptophan load than is cerebral function as reflected in convulsions. Totally speculative in these adult patients must remain the question of time of onset of the abnormal need for vitamin B_6. The published evidence[8] in Harris' case of pyridoxine-responsive anemia suggests development of the condition during young adult life. However, both in the case of the anemia responsive to pyridoxine, and in the patients with convulsions relieved by this substance, the possibility exists of a genetically determined lesion finding its expression later in life.

Japanese investigators have described the production of severe thiamine deficiency in humans by intestinal thiaminase-secreting bacteria.[16] That "pyridoxinase"-secreting organisms might exist and therefore result in abnormally high vitamin B_6 requirement seems a possibility worthy of investigation.

Therefore, dependency on unusually high intake of vitamin B_6 is a rare but apparently well-documented phenomenon, which can make its appearance at any stage of life. Thus far the symptoms of the condition have been either convulsions or anemia, with or without biochemical evidence of pyridoxine deficiency. In general, as in the case of Vitamin B_6-deficient experimental animals, there appears to be a strong tendency for a deficiency of this vitamin to reveal itself by the production of convulsions in young infants, while adults show other manifestations. Present knowledge permits little more than a descriptive discussion of these metabolic lesions, the more exact definition of which must await extensive clinical and biochemical investigation.

REFERENCES

1. Snyderman, S. E., Holt, L. E., Carretero, R., and Jacobs, K.: Pyridoxine deficiency in the human being. *Fed. Proc.* 9: 371, 1950; Pyridoxine deficiency in the human infant. J. Clin. Nutrition 1: 200, 1953.
2. Bessey, O. A., Adam, D. J., Bussey, D. R., and Hansen, A. E.: Vitamin B_6 requirements in infants. *Fed. Proc.* 13: 451, 1954.
3. Bessey, O. A., Adam, D. J., and Hansen, A. E.: Intake of vitamin B_6 and infantile convulsions; a first approximation of requirements of pyridoxine in infants. *Pediatrics* 20: 33, 1957.
4. Coursin, D. B.: Convulsive seizures in infants with pyridoxine deficient diet. *J. A. M. A.* 154: 406, 1954.
5. Molony, C. J., and Parmelee, A. H.: Convulsions in young infants as a result of pyridoxine (Vitamin B_6) deficiency. *J. A. M. A.* 154: 405, 1954.
6. Hunt, A. D., Jr., Stokes, J., Jr., McCrory, W. W., and Stroud, H. H.: Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. *Pediatrics* 13: 140, 1954.

7. HUNT, A. D., JR.: Unpublished observations.
8. HARRIS, J. W., WHITTINGTON, R. M., WEISMAN, R., JR., and HORRIGAN, D. L.: Pyridoxine responsive anemia in the human adult. *Proc. Soc. Exp. Biol. Med.* 91: 427, 1956.
9. ERNSTING, W., and FERWERDA, T. T. P.: Vitamin B_6 in therapy of epilepsy. *Nederl. tidjschr. geneesk.* 95: 3643, 1951.
10. TOWER, D. B.: Neurochemical aspects of pyridoxine metabolism and function. AM. J. CLIN. NUTRITION 4: 329, 1956.
11. GOZZANO, M., and COLOMBATI, S.: Die Virkung der B Vitamine auf das Elektrencephalogram. *Arch. Psychiat.* 183: 192, 1949.
12. GOZZANO, M., COLOMBATI, S., and SINISI, C.: Action des vitamines B sur l' E. E. G. des epileptiques. *Presse Med.* 57: 1072, 1949.
13. COURSIN, D. B.: Effects of vitamin B_6 on the central nervous activity in childhood. AM. J. CLIN. NUTRITION 4: 354, 1956.
14. FOX, J. R., and TULLIDGE, G. M.: Pyridoxine (Vitamin B_6) in epilepsy; a clinical trial. *Lancet* 2: 345, 1946.
15. VILTER, R. W., MUELLER, J. F., GLAZER, H. S., JARROLD, T., ABRAHAM, J., THOMPSON, C., and HAWKINS, V. R.: Effect of vitamin B_6 deficiency induced by desoxypyridoxine in human beings. *J. Lab. & Clin. Med.* 42: 335, 1953.
16. Bacterial Synthesis and Destruction of Thiamine. *Nutrition Reviews* 15: 65, 1957.

Editorial

Man, the Laboratory Animal

In a recent important article on the influence of dietary fats on serum lipid levels in man, Ahrens and his colleagues from the Rockefeller Institute[1] made a particularly pertinent statement: "The unique design of these studies was based on the belief that nutritional experiments can be carried out as precisely in man as in animals."

Their detailed findings suggest that unsaturated fatty acids produce lowering of lipid levels and that this may be related to the number of double bonds (iodine value) in the oils. However, the significance of their findings should be considered in the total view of the experimental design. It is this particular point which motivates this editorial.

In their reported studies, all recognized extra-dietary factors influencing serum-lipid levels were kept to a minimum. The patients were carefully selected and observed in the closely supervised environment of metabolic wards for periods of from four to six months in most cases, and uninterruptedly for as long as 36 months in one patient. Dietary intakes were simplified and rigidly standardized. Even the variable of cooking was eliminated by the feeding of what is known as a formula diet. All the known requirements for essential foodstuffs, minerals, and vitamins were supplied. In addition, medical and hospital care were provided to the patients without charge and constant attention was paid to social-economic factors which "might disrupt their adjustment to the study situation."

Although these subjects were hypercholesteremic or hyperlipemic, all were free from complicating medical conditions and were ambulatory. This is important because so often experiments are carried out on hospitalized subjects who do have conditions complicating long-term metabolic studies.

In a typical feeding experiment, the patient ate an *ad libitum* diet for eight weeks. (This was a truly prolonged control period.) After each change of formula, there was a transition period during which the lipid levels became adjusted. This interval was followed by a new steady stage in which the plateau of serum levels was marked only by minor fluctuations. (The body weight remained unchanged during the study.) The length of the transitional phase was determined on an individual basis by inspection of the data and varied from three days to eight weeks but usually was completed in two or three weeks. Measurements during the transitions were omitted in the calculations. Consequently, with each change in formula, at least the first two weeks' determinations were discarded when selecting data for comparisons.

As noted in an editorial in the same issue of *Lancet*,[2] "Advancement of our understanding of several important pathologic processes would be much accelerated by the study of patients under similarly controlled conditions for periods to be measured in months." Of course, a study of this type involves a tremendous outlay in personnel. To care for and investigate thoroughly five patients, a staff of twenty-five to fifty persons may be necessary. This does not include the problems of floor space for the laboratory and the expensive problem of the accurate collection and analysis of data. The editorial concluded: "Properly safeguarded, *Homo sapiens* can be a very useful laboratory animal."

Along these lines, attention should be called to a recent critique of the conduct of clinical trials in infant nutrition prepared by the

American Academy of Pediatrics.[3] In discussing some of the principles useful in conducting nutritional research the report points out that the type of population for which the conclusion is intended should determine the choice of subjects. Thus the value of foodstuffs for *all* infants should be studied in subjects from a heterogenous population. On the other hand, a dietary supplement for treating a deficiency must be assayed in the deficient subjects for such a supplement would probably produce no significant changes in normal subjects. And even if such changes were effected in normals, these results would not necessarily apply to the treatment of the deficiency.

The problem that nutritional research faces today can be clearly seen in the criteria of measurements in a clinical trial *The aim of good nutrition is the achievement and maintenance of optimal health;*[3] however, there are neither ideal standards of, nor simple methods for, measuring health. Indirect measurements, such as that of total hemoglobin and serum protein, may be useful but certainly are not at all conclusive. Furthermore, maturation rates, as determined by epiphyseal growth, the length of long bones, and dentition, although often used to evaluate pediatric nutrition, correlate rather poorly with height and weight indices. An example of this is the patient with iron-deficiency anemia in whom height and weight may be reasonably normal although epiphyseal maturation is retarded.

Unfortunately, *ideal* patterns for growth of healthy children are not known although there are many studies which provide data of growth averages for selected populations. It may be a debatable point, moreover, whether growth at a rate greater than the average of established groups is beneficial. Thus, an increased consumption of a special diet may accelerate weight gain of normal infants, but this increase may be temporary because the subjects at some later time may stop growing while chronologic age catches up to morphologic age. Therefore, since there are no universally accepted standards for ideal growth in children, each study should provide appropriate growth standards from control subjects and avoid comparing growth of an experimental group with arbitrary growth standards.

Of the criteria used to evaluate nutritional progress, the simplest and least liable to error is rate of weight gain. Unfortunately, this procedure lacks popular appeal, perhaps because there is a "lack of sophistication" in this method.[3] The disadvantages here are readily apparent. These include the absence of a standard for ideal weight gain and the uncertainty as to whether the gain is due to an accumulation of fat or water rather than protoplasmic synthesis.

In addition, because use of published tables on food composition does not always furnish sufficiently accurate data, the diet itself as well as the stool and urine must be analyzed chemically. Finally, publication of basic data, such as variations in replicate determinations and recovery experiments will show the degree of precision of laboratory procedures and will help in the evaluation of the experiment.

Before the details of the experiment are planned, the investigator should determine either from the literature or from a pilot study, the estimates of variation in the control and test groups, and an estimate of the expected differences between these groups at the end of the experiment. Then, after deciding on the level of significance, "it is possible to estimate the minimum number of observations necessary to give the expected differences the desired precision." The interested reader is referred to this article[3] for an example of the calculation of the minimum number of subjects and experimental (balance) periods theoretically necessary in an example in which certain statistical requirements have been established.

It is heartening to see in these interesting papers the development of the concept that nutritional experiments in man can be done with the same precision as they are done in the better animal studies, although it is certainly recognized that at present this is a relatively impractical and expensive procedure for all but a few organizations. Nevertheless, it is significant that a scientific academy felt the need for a "statement of the essential principles governing scientific appraisal of nutritional substances through clinical trials with hu-

mans."[3] It is clearly essential that this new point of view be extended to all investigators in clinical nutrition for it seems obvious that only in such a frame of reference lies the future of research on that most unique of laboratory animals—man.

—S. O. WAIFE, M.D.

REFERENCES

1. AHRENS, E. H. JR., HIRSCH, J., INSULL, W. JR., TSALTAS, T. T., BLOMSTRAND, R., and PETERSON, M. L.: The influence of dietary fats on serum-lipid levels in man. *Lancet* 1:943, 1957.
2. Editorial: Long-term studies in man. *Lancet* 1:977, 1957.
3. LOWE, C. U., and PESSIN, V.: The conduct of clinical trials of substances proposed for the nutrition of infants and children. *Pediatrics* 19:694, 1957.

Letter to the Editor

DIABETIC RETINOPATHY: CORRELATION WITH VITAMIN B_{12} EXCRETION

Dear Sir:

In 1953, Becker, Lang, and Chow demonstrated marked elevation in the urinary excretion of injected vitamin B_{12} in diabetes with retinopathy as compared to non-diabetics and diabetics without retinopathy (J. CLIN. NUTRITION 1:417, 1953).

In view of the difficulty of the microbiologic assay of vitamin B_{12} in urine, a considerable amount of attention was given to validating the experimental and assay procedures with recovery experiments. In addition to the microbiologic assay, using *Lactobacillus leichmannii*, radioactive cobalt-labeled vitamin B_{12} was used as a tracer, and this method gave results which were virtually identical with those of the microbiologic assay.

In a recent paper (AM. J. CLIN. NUTRITION 5:26, 1957), Bookman and his associates report an attempt to reproduce our findings. A number of samples were assayed with three different micro-organisms, but no radioactive tracer studies are reported. Although the data are not presented in sufficient detail to allow fully adequate statistical analysis, the results with one of the micro-organisms *L. leichmannii* seem to yield a significant difference, at the 0.05 level, between diabetics with and without retinopathy, although in the opposite direction from that found in the earlier work. The difference indicated by the ochromonas assay was almost significant at the 0.05 level, but, in contrast with the *L. leichmannii* results, the ochromonas difference was in the same direction as that reported by Becker, Lang, and Chow. (The *L. leichmannii* and ochromonas results of Bookman *et al.* are, of course, significantly different from one another.) We are at a loss to explain the statement by Bookman *et al.*: "No P values of less than 0.1 were found between any groups, indicating a total lack of significance for the average difference found between groups in all three methods."

In view of the considerable variability and inconsistent results of the assays using the different organisms, and the lack of any evidence to validate the procedures, the negative finding reported by Bookman *et al.* cannot be considered to contradict the results of the earlier work.

BACON F. CHOW, PH.D.
BERNARD BECKER, M.D.
CALVIN LANG, A.B.
PAUL MEIER, PH.D.

Department of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland.

Diet Therapy

PLANNING A RESTRICTED SODIUM DIET AND BLAND, LOW-FIBER DIET FOR THE DIABETIC PATIENT

By DORIS JOHNSON, PH.D.*

THE PLANNING of diets for diabetic patients was considerably standardized and simplified when in 1950 the report of a joint committee of the American Dietetic Association, the American Diabetes Association, and the Chronic Disease Program of the U. S. Public Health Service was presented.[1] This report was described in an earlier issue of this JOURNAL.[2] In planning the modern diabetic diet it has now become a widely accepted procedure to use the "Exchange Lists" developed by this committee.[3]

Using the exchange lists in meal planning for the diabetic patient allows him to have an adequate diet with a wide selection of foods. Six basic groups of foods have been described which can be used to plan the day's meals.[3,4] Table I gives the composition of these food exchanges. The foods included within each list are comparable in protein, fat, and carbohydrate values, thus allowing any food in a specific list to be used in the daily diet in the amounts specified in the basic plan. The basic plan for a patient should include at least the minimum amount of each of the groups of foods necessary for an adequate diet.

TABLE I

Composition of Food Exchanges

List	Food	Measures	g	Prot.	Fat	Carb.	Calories
1	Milk exchanges	1/2 pt	240	8	10	12	170
2a	Vegetable exchanges	as desired	—	—	—	—	—
2b	Vegetable exchanges	1/2 cup	100	2	—	7	36
3	Fruit exchanges	varies	—	—	—	10	40
4	Bread exchanges	varies	—	2	—	15	68
5	Meat exchanges	1 oz	30	7	5	—	73
6	Fat exchanges	1 tsp	5	—	5	—	45

Nine basic plans of different caloric value (Table II) have been devised to be used in the planning of diets for both children and adults. Three of these plans numbers 7, 8 and 9 are new additions to the previously prepared materials. Outlines of these plans are available.[5] These materials also appear in the second edition of the *Diabetes Guide Book for the Physician*[6] published by the American Diabetes Association. It cannot be overemphasized, however, that it is absolutely essential that these plans not be given to a patient without adequate oral explanation. There is evidence to show that the degree to which a patient follows a diet is in proportion to the instruction which he has received. The ideal situation is to have the patient receive instruction from a dietitian or nutritionist until he is thoroughly familiar with all phases of his diet. The great majority of patients are unable to fully understand all the possibilities of their diets from printed instructions alone.

Sample meal plans were devised primarily for physicians who do not have available the services of a dietitian or nutritionist to help in

* Director, Dept. of Dietetics, Grace-New Haven Community Hospital, New Haven, Conn.

TABLE II
Total Day's Food in Sample Meal Plans

Meal plan no.	Protein, g	Fat, g	Carbohydrate, g	Calories	Milk exchange (list 1)*	Vegetable exchanges		Fruit exchange (list 3)*	Bread exchange (list 4)*	Meat exchange (list 5)*	Fat exchange (list 6)*
						A (list 2)*	B (list 2)*				
1	60	50	125	1,200	1 pt	As desired	1	3	4	5	1
2	70	70	150	1,500	1 pt	As desired	1	3	6	6	4
3	80	80	180	1,800	1 pt	As desired	1	3	8	7	5
4	90	100	220	2,200	1 pt	As desired	1	4	10	8	8
5†	80	80	180	1,800	1 qt	As desired	1	3	6	5	3
6†	100	130	250	2,600	1 qt	As desired	1	4	10	7	11
7†	140	165	370	3,500	1 qt	As desired	1	6	17	10	15
8	115	130	250	2,600	1 pt	As desired	1	4	12	10	12
9	120	145	300	3,000	1 pt	As desired	1	4	15	10	15

* See *Meal Planning with Exchange Lists.*[3]

† These diets contain more milk and are especially suitable for children.

the basic planning of the day's diet for the patient. Again, it is more ideal, if at all possible, to make a basic plan to fit the needs of each individual patient, taking into consideration his hours of work, nationality, religious customs, and economic situation.

Table III reproduces from the Diabetic Diet Card for Physicians[4] the rationale for the selection of the dietary prescription for the patient. It is to be noted that the caloric needs, based on actual weight in relationship to desired weight, activity, and body size, is the determining factor in the selection of a diet plan. It is to be further noted that the patient's weight should be followed regularly to determine whether or not the proper caloric level has been selected, and any necessary adjustments should be made accordingly.

Another point which should be emphasized at this time is that it is not necessary to weigh diabetic diets. Measurement by household measures is entirely adequate. The accuracy implied by weighing a diet in grams is not warranted. The composition of a specific food may vary sufficiently from the average figure given in food composition tables as to make such accurate weighing meaningless. Furthermore, the daily bodily requirements and utilization of food also fluctuate considerably depending upon various circumstances, but in particular, the activity and emotional state of the individual.

MODIFIED DIABETIC DIETS

The diabetic patient may have other complications along with his diabetes which are also amenable to further dietary modifications such as restriction of sodium or a bland, low-fiber diet. In order to simplify the planning of such combination diets, modifications of the exchange lists have been prepared.[7,8,9] Modifications of the exchange lists for a restricted sodium diet and for a bland, low-fiber diet follow. These new modifications of the exchange lists should help considerably to eliminate confusion for the patient in attempting to make a dual modification of his diet.

MODIFICATIONS OF EXCHANGE LISTS TO PERMIT SODIUM RESTRICTION

Follow your "Meal Planning with Exchange Lists" with the changes listed below. *Add no salt in cooking or at the table.*

List 1—Milk Exchanges

Average sodium: 120 mg per Exchange (1/2 pt).

Up to 1 pt milk is allowed. If your diet calls for more than 1 pt milk, use low-sodium milk (a special commercial product). Avoid any foods prepared with milk unless taken from the amount allowed for the day.

List 2—Vegetable Exchanges

Average sodium: 9 mg per Exchange (1/2 cup).

Use only *fresh* vegetables unless you are certain no sodium has been added to the canned or frozen ones.

(A) Select *only* from the vegetables listed below:

- Asparagus
- Broccoli
- Brussels sprouts
- Cabbage
- Cauliflower
- Chicory
- Cucumbers
- Escarole
- Eggplant
- Endive
- Green beans
- Green peppers
- Lettuce
- Mushrooms
- Okra
- Radishes
- Summer squash
- Tomatoes
- Turnip greens

(B) All vegetables on this list are allowed *except* beets, carrots, and turnips.

List 3—Fruit Exchanges

Average sodium: 2 mg per Exchange.

All fruits are allowed. Raisins and dried figs have a higher sodium content than other fruits. Since the size serving allowed is small, they may be used.

List 4—Bread Exchanges

Average sodium: 5 mg per Exchange.

Use *only* home-made or bakery-made breads and rolls prepared without salt, milk, or salted fat. The following "quick breads" are permitted *provided* they are made with low-sodium baking powder: cornbread, rolls, muffins, and biscuits. Select *only* from the foods listed below:

Beans or peas, dried—1/2 cup cooked
Corn, fresh or frozen (unsalted)—1/3 cup
Grits—1/2 cup
Lima beans, fresh—1/3 cup
Macaroni—1/2 cup
Matzoth, unsalted—1 (6 in. diameter)
Muffets—1 biscuit
Noodles—1/2 cup
Oatmeal—1/2 cup
Parsnips—2/3 cup
Popcorn, unsalted—1 1/2 cup
Potato—1 (2 in. diameter)
Puffed Rice—3/4 cup
Puffed Wheat—3/4 cup
Ralston—1/2 cup
Rice—1/2 cup
Shredded Wheat—2/3 biscuit
Spaghetti—1/2 cup
Sweet potato—1/4 cup
Wheatena, regular—1/2 cup

List 5—Meat Exchanges

Average sodium: 25 mg per Exchange.

All varieties of meat, fish, or poultry are allowed *except* shellfish (clams, oysters, shrimp, lobster), brains, kidney, and heart. One egg a day is allowed. *Omit* all smoked, salt-cured, dried, canned, and kosher-cured meats or fish, including: cold cuts, frankfurters, sausage, ham, corned beef, and so on. *Omit* all types of cheese except "salt-free" cottage and Cheddar cheese. *Omit* peanut butter, unless it is a special, low-sodium variety. Low-sodium tuna fish and salmon are available in some stores.

List 6—Fat Exchanges

Average sodium: negligible.

All fats must be "salt free." Unsalted butter, margarine, fats, and oils are allowed. *Omit* bacon, salt pork, mayonnaise, salad dressings with added salt, salted nuts, and olives.

Condiments and Flavorings That May Be Used

Allspice	Horseradish root	Pimento
Almond extract	Juniper	Poppy seeds
Aniseed	Lemon juice	Poultry seasoning
Basil	Mace	Purslane
Bay leaves	Marjoram	Rosemary
Calcium Sucaryl	Mint	Saccharine
Caraway seeds	Mustard, dry	Saffron
Cardamon	Onion juice, fresh	Sage
Cinnamon	Oregano	Savory
Cocoa (1–2 tsp.)	Paprika	Sesame seeds
Chili powder	Parsley	Sorrel
Chives	Pepper (black, red, and white)	Tarragon
Curry powder	Peppermint	Thyme
Dill		Tumeric
Garlic		Vanilla extract
Ginger		Vinegar

Do Not Use These Foods

(for other restrictions, see notes above under separate Exchange Lists)

Baking powder	Mustard, prepared
Baking soda	Onion salt
Bouillon cubes	Pickles
Celery salt	Potato chips
Garlic salt	Pretzels
Horseradish, prepared	Relishes (commercial)
Ketchup	Salt (table)
Meat extracts	Self-rising flour
Meat sauces	Soups, canned
Monosodium glutamate	Worcestershire sauce

Also certain "stomach antacids," laxatives, and sedatives contain sodium and are not recommended.

Special Sodium-Restricted Dietetic Foods

Foods specially processed without salt or other sodium products for use with sodium-restricted diets are available. By law, the labels on these foods must state the amount of sodium in 100 g or for an average portion.

MODIFICATION OF EXCHANGE LISTS FOR BLAND, LOW-FIBER DIET

Follow your "Meal Planning with Exchange Lists" with the following changes:

List 1—Milk Exchanges

Allowed in amounts prescribed in diet. Any form of milk is desirable (1 oz Cheddar cheese and 2 soda crackers may be used for 1 cup [8 oz] milk).

List 2—Vegetable Exchanges

Omit raw vegetables. Use *only* vegetables in the following list:

(A)	(B)
Asparagus tips	Beets
Chard	Carrots
Spinach	Peas
Squash, summer (without seeds)	Pumpkin
String beans, young	Squash, winter
Tomato juice	
Tomato purée, unseasoned	

In special cases, the physician may recommend strained or puréed vegetables.

List 3—Fruit Exchanges

Fruits should be cooked or canned unsweetened. The only fresh fruits allowed are marked with an asterisk. Avoid all skins or seeds. Select *only* the fruits listed below in amounts given in the "Meal Planning" booklet.

Applesauce or baked apple	Grapefruit juice
Apricots, fresh	*Orange juice
Apricots, dried	Peach
*Banana	Pear
Cherries, canned	Pineapple juice
	Plums, canned
	Prunes

In special cases, the physician may recommend strained fruits.

List 4—Bread Exchanges

Only *white*, refined breads, cereals, or crackers are allowed. Potatoes, sponge cake, and ice cream in measured amounts are also allowed. *Omit* corn, parsnips, dried beans, and dried peas.

List 5—Meat Exchanges

Use only tender cuts (whole, ground, or chopped) of beef, veal, lamb, pork, chicken, or liver. The following fish are allowed: cod, haddock, halibut, and similar white fish; salmon; tuna; and shellfish. Eggs, Cheddar and cottage cheese, and creamy peanut butter are allowed. *Omit* cold cuts, frankfurters, and sausages.

List 6—Fat Exchanges

Butter, margarine, cream, cream cheese, and bacon are the only foods allowed on this list.

In special cases, your physician may wish to make recommendations regarding the use of fried foods, tea, coffee, meat broths, and highly seasoned foods.

SODIUM

The average sodium content of the various groups of foods in the exchange lists is indicated above and the average sodium content of the various plans is given in Table IV. Note that the milk and meat exchanges furnish the greatest amount of sodium. The sodium figures given for the various plans are on the basis of one pint of regular milk. If more milk is allowed in the diet plan, then some

TABLE III

Selection of the Dietary Prescription

A dietary prescription is based on the caloric needs of the patients. Caloric requirements are influenced by present weight in relation to desirable weight, activity, and body size. It is recommended that the desirable weight table be used and that an appraisal be made of the usual amount of activity in which the patient is involved. Then, select the dietary prescription best suited for the patient.

Adults

Weight and activity of patient	Height below 5′ 6″		Height above 5′ 6″	
	Caloric prescription	Corresponding meal plan no.	Caloric prescription	Corresponding meal plan no.
Ideal weight				
Sedentary	1,800	3	2,200	4
Moderately active	2,600	8	3,000	9
Very active	3,000	9	3,500	7
Overweight				
Sedentary	1,200–1,500	1 or 2	1,500–1,800	2 or 3
Moderately active	1,800	3	2,200	4
Very active	2,200	4	2,600	8

Children

The selection of the dietary prescription for children is more difficult than for adults. Sufficient calories must be supplied for proper growth and development and to meet energy needs. Diets for children at different ages and with different caloric requirements can easily be developed by adding additional amounts of the food exchanges, especially the Bread and Meat Exchanges (lists 4 and 5) which provide approximately 70 calories per exchange.

Age of child	Caloric prescription	Corresponding meal plan no.
About 8 yr	1,800	5
10 to 12 yr and girls 13 to 18 yr	2,600	6
Boys 13 to 18 yr	3,500	7

It is most important to realize that a periodic check-up is the only way to determine whether the prescribed diet is meeting or exceeding the caloric needs of the patient. On the basis of this observation, adjustments in the caloric level of the diet may be needed.

TABLE IV

Average Sodium Content of Sample Meal Plans 1 through 9

Meal plan no.	Sodium content *mg*	Sodium chloride content *g*
1, 2, 3, and 4	400–500	1
5, 6, and 7	700–850	2
8 and 9	600	1½

form of low-sodium milk must be used. It is also noted that if a diet lower in sodium than that given for the plan is desired, a low-sodium milk may be used in place of regular milk. Since one pint of milk contains about 240 mg of sodium a considerable reduction in sodium is possible by this substitution. It should be pointed out, however, that low-sodium milks generally are quite unpalatable and such restricted diets are not easily followed by the patient. Furthermore, the rationale for such a restricted sodium regimen should be well considered by the physician before the diet is "inflicted" on a patient.

In planning a restricted sodium diet it is essential to avoid all sources of sodium. For example the water used in food preparation and for drinking should be analyzed. Some water supplies are naturally high in sodium while softened waters may be a considerable source of sodium and, if used, can make a well-planned restricted-sodium diet of no value for therapeutic purposes. Medications containing sodium, of course, cannot be used.

It is essential too to use only those foods listed in each of the modified exchange lists in the amounts allowed if the sodium level is to be maintained within the general range given for that diet plan. The lists compiled are based on figures from the National Academy of Sciences-National Research Council publication No. 325[10] which also includes a complete discussion of sodium-restricted diets. This pamphlet is recommended reading for all physicians before prescribing a sodium-restricted regimen.

BLAND, LOW-FIBER DIETS

The modification of the exchange lists so that a bland, low-fiber diet may be planned, as herein given, allows for a liberal interpretation of this regimen; the trend in the planning of this diet is in this direction. Individualization of this regimen is extremely important since foods found troublesome for one patient are not necessarily so for another. The degree to which the foods must be modified in form, i.e. puréed, strained, or chopped instead of left whole, will depend upon the condition of the patient and the discretion of the physician. The general principles of the bland, low-fiber diet as presently accepted however, should be borne in mind. These are that the bland regimen should be mechanically, chemically, and thermally non-irritating.[11] The modifications of the exchange lists are such as to carry out these principles. However, undue restrictions are to be avoided and the diet should be individualized to meet the patient's needs.

It should be kept in mind that either of these modifications of the diabetic diet, sodium restriction or bland, low-fiber, results in a considerable limitation in a patient's selection of foods. The patient needs much help and encouragement to carry out such restricted regimens.

SUMMARY

Additions to previously prepared meal-planning materials for diabetic patients have been made available. These include three sample meal plans at higher caloric values, and outlines for two modifications of the exchange lists so that sodium-restricted or bland, low-fiber regimens may be planned.

REFERENCES

1. Caso, E. K.: Calculation of diabetic diets. *J. Am. Diet. A.* 26: 575, 1950.
2. Johnson, D.: Planning the modern diabetic diet. J. Clin. Nutrition 1: 309, 1953.
3. Am. Diabetes A., Am. Dietet. A., and Chronic Disease Program, Public Health Service: *Meal Planning with Exchange Lists*, Am. Dietet. A., Chicago, 1956.
4. Am. Diabetes A., Am. Dietet. A., and Chronic Disease Program, Public Health Service: *Diabetic Diet Card for Physicians*, Am. Dietet. A., Chicago, 1956.
5. *Meal Plans No. 1 through 9*, Am. Dietet. A., Chicago, 1956.

6. Committee on Education: *Diabetes Guide Book for the Physician*, ed. 2, Am. Diabetes A., New York, 1956.

7. Supplements to diabetic diet material. *J. Am Diet. A.* 32: 929, 1956.

8. *Sodium-Restricted Diabetic Diet Modification*, Am. Dietet. A., Chicago, 1957.

9. Caso, E. K.: *Bland, Low-Fiber Diabetic Diet Modification*, Am. Dietet. A., Chicago, 1957.

10. Committee of the Food and Nutrition Board: *Sodium-Restricted Diets*, Publ. 325, National Academy of Sciences-National Research Council, Washington, D. C., 1954.

11. Johnson, D.: The bland diet in ulcer therapy. *J. Am. Dietet. A.* 23: 686, 1947.

Reviews of Recent Books

Modern Problems in Pediatrics II, by A. Hottinger and F. Hauser. S. Karger, Basel, 1957, pp. 222, Sw. Fr. 32.

This book is a report of a symposium on the "Physiology and Pathology of Digestion in Infancy" held in the Children's Hospital at Basel, Switzerland from August 1 to 3, 1956. Participants were pediatricians from various countries throughout the world who had attended the International Congress of Pediatrics in Copenhagen in July.

A total of 18 papers are presented, most of which are followed by the general floor discussion. Seven of the 18 papers are in English, ten in German, and one in French. Two of the German papers have brief summaries in English. It would have been helpful to potential readers not conversant with German or French, if all had been similarly treated.

This symposium dealt only with problems related to the gastrointestinal tract. György discussed the intestinal flora in human milk-fed infants and described his discovery of a specific mutant of *L. bifidus* which was named *L. bifidus var. pennsylvanicus*. He concluded that the role of *L. bifidus flora* in the physiology of the human milk-fed infant is still shrouded in mystery, but expressed the hope that the beginning which has been made may lead to a better understanding of the problem.

Holt reported upon his studies on fat absorption in infants. Most important of these, he believes, is the observation that the quantity of fat absorbed appears to be proportional to the intake, even though absorption is very inefficient, as for instance in diarrhea.

To this reviewer, the paper contributed by Dean from Kampala, Africa, on digestion in kwashiorkor, is of special interest. In describing the pathology of the digestive organs in a child who has died of kwashiorkor the author makes the startling statement that the walls of the small intestine may be so "diaphanous that print can easily be read through them," and that the pancreas may be so reduced in size that it is a "small cord stretching from the duodenum to the spleen." His further observations on the therapeutic attempts with various types of diet are most enlightening.

It is not possible in this brief review to summarize each paper. Suffice it to say that a wide variety of topics were covered which included intestinal allergy, pathology of parenteritis, pathogenic intestinal bacteria, absorption of various types of lipids, and metabolic disturbances. The authors are to be congratulated for their industry in seizing upon the opportunity to bring together a group of international experts for an exchange of views and for publishing the proceedings in book form. As stated previously the value of the book to many Americans could have been enhanced by the inclusion of abstracts in English.

LEE FORREST HILL

Analytical Microscopy. Its Aims and Methods in Relation to Foods, Water, Spices, and Drugs, by T. E. Wallis, Little, Brown, & Co., Boston, 1957, pp. 215, $5.50.

This is the second edition of a book that originated in a series of articles first published in the *Pharmaceutical Journal* more than thirty years ago. It has more than double the illustrations of the original work. The book gives methods for preparation of materials for microscopic examination and is surprisingly encyclopedic for its size. Bacteriology and crystallography are deliberately omitted, however. The text represents a commendable effort toward providing, as a substitute for a broad knowledge of biologic structures, a manual of procedures, descriptions, and illustrations with a profusion of original drawings.

Three-quarters of a microscopist's time might be spent in preparing material for examination. The textbook covers this area by giving minutiae of procedures for sifting powders for seeds and vegetable fragments, as well as part of contaminating insects. Procedures for preparation and sectioning of mixtures of leaves, barks, seeds, and fruit (as in the culinary herbs) are described; plant anatomy of pertinent species is given in detail. A whole chapter is devoted to the technology of sedimentation and centrifugation, primarily for taxonomic aspects of limnology, but also for sediments in liquids other than water. For example, kneading flour or starch in a cloth bag under water gives a variety of different types of sediments for examination; the chapter on that subject describes typical findings. On the other hand, the technic of concentration (elutriation) is really a differential centrifugation procedure that can be used to examine rice for facing, or to establish the foraminiferous origin of a chalky limestone. The nature of the starch of sago or tapioca can be determined by elutriation. The chapter on elutriation discusses the treatment of jams and honeys by water solvent to identify the source of origin.

A general chapter on solvents and clearing agents is interwoven with the morphology and mounting methods for insects and mites, as well as the identification of canned fish, or fish pastes by scale characters. Chemo-

microscopy reagents and their applications are discussed in another section; miscellaneous tests for applepulp in jam, nutmeg in powdered mace, calcium carbonate in calcium oxalate, blood, etc., are described.

The chapters on sublimation, precipitation, and staining, as well as the chapter on quantitative microscopy, might well have followed, but are separated from chemomicroscopy by a section on micromorphology. However, many nonbiologic materials can be conclusively identified by use of the microscope. Precipated sulphur may be differentiated from sublimed sulphur by such procedures.

The remainder of the text is comprised of discussions of methods of measurement, illustration, and photography, plus an appendix of miscellany. An invaluable bibliography contains references as recent as January 1956, but much space is taken up with unavailable publications. Other references are given in the text of the book. The index could be more comprehensive. Despite these limitations, this textbook should prove a welcome addition to the bookshelf of the food and drug laboratory. ELI COHEN

Annual Review of Medicine, Vol. 8, edited by D. A. Rytand. Annual Reviews Inc., Palo Alto, 1957, pp 478, $7.00.

The 1957 edition of Annual Review of Medicine continues in the best traditions of this distinguished series. The section on nutritional problems was written by M. I. Grossman, who does a commendable job based on some 124 references. Certain recent advances in the study of liver disease, amino acid requirements, cholesterol, and obesity are presented.

This issue has a number of chapters devoted to somewhat neglected topics including rentrolental fibroplasia, pneumoconiosis, helminthic diseases, and drug addiction. As usual the authors have all had extensive experience in their fields and an obviously wide familiarity with the literature.

It is apparently customary for book reviewers to make some constructive criticism, and in this case one would comment that the Annual Reviews would be even more valuable if there were more frequent reference to the foreign literature. Certainly this would be a boon to the investigator who is presumably the reader benefiting most from these excellent reference volumes. No doubt the embarrassment of riches representing the vast medical literature makes the preparation of these reviews a difficult task. Nevertheless we must not be medically chauvinistic and limit ourselves to English language science. With this comment noted the book can be strongly recommended to all engaged in teaching and research. S.O.W.

The Yearbook of Endocrinology (1956–1957 Year Book Series), edited by Gilbert S. Gordon. The Year Book Publishers, Chicago, 1957, pp. 377, $6.75.

There are many points at which the sciences of endocrinology and nutrition meet in the study of human and experimental metabolism and biochemistry. Rapid advances in endocrine chemistry have revolutionized earlier concepts of hormone actions and have added new substances of particular interest to physicians engaged in the study of nutrition. The current Year Book of Endocrinology effectively distills the important contributions in this field during 1956 into a single volume. The six sections of the book are devoted to the pituitary, thyroid parathyroid glands, and metabolic bone diseases, the adrenal glands, the reproductive system, and carbohydrate metabolism. There are two original contributions, one by Elrick dealing with recent developments with glucogen and one by E. C. Albright and Larson on thyroid hormone transport. These discussions are thorough and succinct, bringing the reader abreast of the latest knowledge available in these areas of metabolic research. The delightful interpolations of the editor following many of the abstracts greatly enhances the value of this book.

The nutritionist will be particularly interested in the discussions on calcium and phosphorus metabolism, hormonal influences upon lipid and cholesterol levels, and upon nitrogen and carbohydrate metabolism, and the recent concepts of the effects of aldosterone upon electrolytes. This is a book which will serve as an excellent reference for the significant articles of the past year in clinical and investigative endocrinology.

C.R. SHUMAN

Body Measurements and Human Nutrition, edited by Josef Brožek. Wayne University Press, Detroit, 1956, pp. 167, $3.50.

Anthropometry has the very real potentiality of contributing to the advancement of nutrition, especially in providing a better basis for the physical characterization of an individual. This would be especially desirable in evaluating the degree of leanness and obesity. During the past few years, a committee established by the Food and Nutrition Board of the National Research Countil has been considering the anthropometric measurements which might be most useful in nutrition work. The final act of the committee was to sponsor a conference at Harvard University in June 1955 at which the minimum anthropometric measurements which should be used in assessing the nutritional status of an individual were agreed upon by those attending the conference. The first chapter of the book presents these for both adults and children, with the various measurements indicated as being those that are the least that should be included in any set of measurements, those that should be added as a minimum for nutritional survey work, and those that would be desirable for surveys.

The remainder and by far the larger part of the book is given over to a series of reports by the conferees on studies that have utilized one or more anthropometric procedures. In the first of these Brožek presents the correlations between a variety of anthropometric measurements and body weight. The skinfold thick-

nesses of Minneapolis firemen are given for the upper arm and subscapular area. An interesting observation is that although only 20 per cent of the Minneapolis firemen had arm skinfolds of 9 mm or less, 51 per cent of Sardinian policemen, 56 per cent of Cape Town colored, and 60 per cent of Cape Town Bantu fell in this group.

R. M. White presents body weights and heights and a number of other anthropometric measurements of 2,650 25-year-old white men who were discharged from the Army in 1946. Each man was characterized as small, medium, or large, on the basis of both chest width and bi-iliac diameter. The mean body weights for different heights were given for each of these groups. The maximum weights listed in the Metropolitan Life Insurance Company's table for men with small, medium, and large frames approximated the mean weights of the Army men segregated on the basis of bi-liac diameter.

M. Trotter examined 24 male skeletons of individuals ranging from 18 to 87 years of age and found a high correlation between the weight of the femur and the total weight of the skeleton. The male American Negro was reported by R. W. Newman to be leaner than his white counterpart as shown by a study of a large group of young men on discharge from the Army. Pascale and co-workers present a multiple regression equation for the calculation of body density in young men from skinfold thicknesses as measured on the chest, abdomen, and upper arm. L. B. Pett and G. F. Ogilvie report on the height-weight survey recently completed in Canada. M. A. Ohlson and co-workers provide a preliminary report on a variety of anthropometric measurements of adult women in the North Central states. A. B. Kurlander and associates report that among a group of Negro patients at the municipal hospital in Washington, D. C., the excess mortality of overweight men could not be correlated with their body fat content as determined by a variety of anthropometric measurements. This report is followed by a defense of life insurance statistics by H. M. Marks. S. M. Garns and associates report that the amount of fat in an infant at birth provided no reliable indication of the changes in this body component during the first year of life. E. E. Hart and E. Giles discuss the changes that occur in the concentration of water and fat in growing animals and children.

The book provides a great deal of information which will be of interest to workers in human nutrition. It is hoped that the investigators making anthropometric measurements on human subjects will follow the recommendations in the introduction to the work. By this means it may be possible to compare in a more rational way the results of different studies.

OLAF MICKELSEN

Regulation and Mode of Action of Thyroid Hormones. Ciba Foundation, Colloquia on Endocrinology, Vol. 10, edited by G. E. W. Wolstenholme and E. C. P. Millar. Little, Brown, Boston, 1957, pp. 311, $8.50.

Among the participants in the symposium on the thyroid hormone and iodine metabolism are leading investigators from many parts of the world whose contributions have helped to clarify some of the obscure problems in thyroidal physiology. The first seven papers deal with various aspects of the regulation of thyroid activity. Considerable attention is paid to the role of the hypothalmus in the control of the thyroid gland through the anterior pituitary gland. In studying this system a number of investigators have used the iodine (I^{131}) output method for observing changes in thyroid activity in the rabbit. The effects produced by adrenalectomy, steroid hormone and goiterogen administration, hypothalmic lesions and other conditions upon this aspect of thyroid function were described with several new hypotheses being offered to explain the observations. Brown-Grant, in presenting the Feed-Back Hypothesis, suggests that the release of thyrotropin from the anterior pituitary is regulated by the amount of thyroid hormone reaching this site through the portal system emerging from the hypothalmus. Modification of the thyroxine content of the blood supplying the anterior pituitary may adequately explain many experimental and clinical observations in thyroidology.

The metabolism and actions of thyroid hormone are discussed in the remaining twelve contributions. The enzymic formation of tetra- and tri-iodinated thyroacetic acids and the ability of these derivatives to increase immediately oxygen consumption of the animal are described. Because of the several modifications of the hormone which have been described in the gland itself as well as in the tissues, it seems more correct to refer to the thyroid hormones. It is possible that each of these active derivatives is specific for particular functions attributed to the thyroid secretions. The intricate problems of the mechanisms involved in the formation of these derivatives such as deiodination or side chain modifications are discussed as are their modes of action, not only upon tissues but upon cell fractions and enzyme systems.

This text provides a detailed account of the most recent experimental advances in iodine dynamics and thyroid function. Each of the authoritative papers is followed by a thorough and uninhibited discussion by the participants. This serves to broaden the entire presentation.

C. R. SHUMAN

The Importance of Overweight by Hilde Bruch, W. W. Norton, New York, 1957, pp. 412, $5.95.

The author of this significant book has devoted much time and thought to the understanding of obesity from the psychologic standpoint. Her contributions are major milestones in the "psychosomatic" approach to this complex subject. In this readable survey, there is a thorough discussion covering the various psycho-bio-

logic reaction patterns which underlie the pathogenesis of obesity. If her theme can be summarized, it is that there should be a more serious and respectful approach toward the obese. Effective treatment, furthermore, is made unnecessarily difficult because of the derogatory social attitude toward corpulence. Because of unfavorable early experiences and conditioning obese people often lack a strong sense of self, with a continuous damage to their self-esteen by a punitive environment. What is greatly needed is a more accepting and encouraging social climate.

Although there is some discussion of physiologic, endocrine, and metabolic aspects of obesity, including the basal metabolism, the largest and the best portion is devoted to the interpersonal milieu surrounding the obese subject. Since much of the author's work has been with children, the obese child is perhaps the core of the clinical material. This is as it should be because our understanding of obesity will come from our appreciation of how or why obesity develops. The gleanings from chronically obese adults may be more meager.

Two aspects with which the practicing physician may be relatively unfamiliar are the Family Frame and the Cultural Frame; in chapters of the same name these subjects are greatly clarified. Because eating is a lifelong social matter we cannot recognize the complex interactions of modifying factors unless we understand the family background and the culture in which the subject participates.

There are perhaps three general aspects to clinical obesity: environmental forces, psychologic responses, and physiologic reactive patterns. We need to know more about all three before we can answer, "Why is Mary fat?" This book, in its persuasive style, suggests that with our present knowledge we could do more in therapy if we took the time to investigate and reflect on each obese patient. Bruch believes, however, that "only those overweight people who are emotionally well enough to carry it through should undertake a reducing regime." While a reader schooled in the traditional strict-dieting-for-obesity concept may be dissatisfied with this conclusion, some honest analysis will convince him that there may be better ways of treating obese people than by the traditional standard diets and depressing cycle of weight loss and rapid regaining. As the author says, the need for a radical re-evaluation of every aspect of the obesity problem is real and urgent.

Clinicians, even if not psychiatrically oriented, will find this important book useful in practice. It is full of examples of typical cases which will be all-too-familiar to the physician. In addition, there are interesting practical hints. Thus there is an enlightening discussion of the significance of the patient's answer to the question "What difference will it make for you to be fat or thin?" The author deserves warm praise for her preparation of a strong thesis of the psychologic significance of obesity. S.O.W.

Books received for review by THE AMERICAN JOURNAL OF CLINICAL NUTRITION are acknowledged in this column. As far as practicable those of special interest are selected, as space permits, for a more extensive review.

Obesity: Its Cause, Classification and Care by E. P. Gelvin and T. H. McGavack, Hoeber-Harper, New York, 1957, pp. 146, $3.50.

Vitamin A by Thomas Moore, Elsevier, Houston, 1957, pp. 645, $14.00.

Experiments in Biochemical Research Techniques by Robert W. Cowgill and Arthur B. Pardee, John Wiley & Sons, New York, 1957, pp. 189, $3.50.

Health, Success and Happiness for You by Irwinn F. Krimm, Vantage Press, New York, 1957, pp. 247, $3.50.

Health Yearbook 1956 by O. E. Byrd, Stanford University Press, Stanford, Calif., 1957, pp. 278, $5.00.

The Premature Baby by V. Mary Crosse, Little, Brown and Co., Boston, 1957, pp. 242, $5.00.

Swine Feeding and Nutrition by T. J. Cunha, Interscience, New York, 1957, pp. 296, $5.00.

It Pays to be Healthy by R. C. Page, Prentice-Hall, New York, 1957, pp. 285, $4.95.

Cholesterin Ernährung Gesundheit by W. Halden and L. Prokop, Verlag Urban & Schwarzenberg, Berlin, 1957, pp. 80, Sw. Fr. 20.

Essentials of Fluid Balance by D. A. K. Black, Charles C Thomas, Springfield, Ill., 1957, pp. 123, $3.75.

Methodology of the Study of Ageing, edited by G. E. W. Wolstenholme and C. M. O'Connor (Ciba Foundation Colloquia on Ageing, Vol. 3), Little, Brown, and Co., Boston, 1957, pp. 196, $6.50.

Biochemistry of the Amino Acids by Alton Meister, Academic Press, New York, 1957, pp. 485, $10.00.

The Physiology and Biochemistry of Lactation by S. J. Folley, Charles C Thomas, Springfield, Ill., 1957, pp. 153, $3.75.

Degenerative Changes in the Sternoclavicular and Acromioclavicular Joints in Various Diseases by Anthony F. DePalma, Charles C Thomas, Springfield, Ill., 1957, pp. 178, $5.50.

Practical Nutrition by Alice B. Peyton, Lippincott, Philadelphia, 1957, pp. 379, $3.60.

Basic Nutrition by E. W. McHenry, Lippincott, Philadelphia, 1957, pp. 389, $5.00.

Nutrition News

Fourth International Congress of Nutrition

Under the auspices of the International Union of Nutritional Sciences, the Fourth International Congress of Nutrition was held in Paris from July 27 to August 1, 1957, under the presidency of Professor E. F. Terroine.

The meeting was a huge success and the attendance (about 1,000) was larger than expected. Scientists active in nutrition came from all over the world. Representatives from 39 countries, including the U.S.S.R., were present. In all, 350 papers were read. The program was divided into subsections on nutrition and lactation reproduction, skin, digestive tract, senescence, with one devoted to miscellaneous items.

The opening session was addressed by Professor Terroine, Director, National Center for the Coordination of Study and Research on Nutrition; Dr. E. J. Bigwood, President of the International Union of Nutritional Sciences; Dr. W. R. Aykroyd, Chief of the Nutritional Division of F.A.O.; and Dr. R. C. Burgess, Chief of the Nutrition Division of WHO.

The next Congress will be held in September 1960 in Washington, D. C., under the presidency of Dr. C. G. King, assisted by Dr. W. H. Sebrell and Dr. Paul György.

H. GOUNELLE, M.D.
Corresponding Editor
General Secretary, International
Union of Nutritional Sciences

Conference on Nutrition

A conference on nutrition in relation to disease will be held September 30, 1957, at the College of Physicians of Philadelphia. Dr. Floyd S. Daft, Director, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, will speak on "The Relationship between Hormones and Nutrition." Dr. Edward H. Ahrens, Jr., of the Rockefeller Institute of Medical Research, New York, will speak on "Fat Metabolism in Relation to Cardiovascular Disease—Atherosclerosis." The Conference is sponsored by the Commission on Nutrition of the Medical Society of the State of Pennsylvania, the Philadelphia County Medical Society, and the National Vitamin Foundation. Dr. Michael G. Wohl and Dr. Robert S. Goodhart will chair the evening session.

"The ancient art and burgeoning science of medicine knows no national or racial distinctions. Medicine, like art and music, speaks with a human tongue, and its knowledge and technics are dedicated to all mankind."
—Editorial, World Medical Journal 3: 148, 1956.

Abstracts of Current Literature

CHARLES R. SHUMAN, M.D., EDITOR

MARGARET W. BATES, D.SC., *Toronto*
ELIAS COHEN, PH.D., *Buffalo*
A. B. EISENSTEIN, M.D., *St. Louis*
K. R. CRISPELL, M.D., *Charlottesville*
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F. E. HYTTEN, M.B., B.S., PH.D., *Aberdeen, Scotland*
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BARNETT SURE, PH.D., *Fayetteville*
JOHN WATERLOW, M.D., *Kingston, Jamaica*

PANTOTHENIC ACID DEFICIENCY

One of the most important biochemical reactions in cellular metabolism is that involving the formation of acetyl coenzyme A. The coenzyme which functions as an acetate acceptor or donor is an essential catalyst, formed in part of pantothenic acid. Because of its wide distribution in all living things, it is doubtful that nutritional deficiency states involving this vitamin occur except under most unusual conditions. By the use of a metabolic antagonist, pantothenic-acid deficiency has been produced in man. The clinical findings were indicative of interference with adrenocortical function and disturbance of neural activity. These findings correspond to some of the observations made previously on pantothenate-depleted animals.

Pantothenic Acid Deficiency in Human Subjects. W. B. Bean, R. E. Hodges, and K. Daum. *J. Clin. Investigation* 34: 1073, 1955.

This is the follow-up detailed report on the findings previously reported in a preliminary manner in 1954. It deals with the observations made on four young, healthy volunteers in whom pantothenic-acid deficiency was induced by tube-feeding a synthetic diet plus 500 mg per day orally of a pantothenic-acid antagonist, omega-methyl pantothenic acid. The experiment as originally planned was to be divided into three periods; however, as is so often the case in clinical investigation, this plan was altered so that five periods were utilized. These consisted of the following: Period I—Special Diet, devoid of pantothenic acid, fed by stomach tube, and completely supplemented by vitamins, including pantothenic acid, 16 days; Period II—Special Diet without pantothenic acid plus 500 mg of omega-methyl pantothenic acid orally per day, 25 days; Period IIIa—Same as II with 4,000 mg of pantothenic acid added, 6 days; Period IIIb—well balanced normal diet, 2,000 mg of pantothenic acid per day, increased amounts of other vitamins and no antagonist, 10 days; IIIc—Same as IIIb except that synthetic diet was re-instituted.

Although the clinical picture in these persons varied considerably, the following abnormalities were noted. There was a marked physical and mental depression with wide swings in mood. Neuromotor abnormalities occurred which had aspects of peripheral neuritis but may well have been muscular in nature. Some vasomotor instability was seen, postural and vasodepressive in nature. Repeated infections were common and consisted primarily of pharyngitis and lobar pneumonia in one patient. These clinical symptoms were not relieved promptly by pantothenic acid, thus necessitating the change in the plan which included discontinuing the antagonist as well as the special diet and the addition of cortisone.

Biochemical studies were performed and revealed abnormalities in acetylation (using PABA), carbohydrate metabolism (increase in insulin sensitivity, slight decrease in glucose tolerance), blood cholesterol (fall in plasma level and esters), serum proteins (rise in alpha 1 and alpha 2 globulin with fall in gamma globulin) and adrenal function (fall in 17—ketosteroids and decreased eosinophil response to ACTH). Again, these abnormalities were quite variable from patient to patient.

The authors believe that these experiments indicate that pantothenic acid is an essential nutrient for human beings. This study, utilizing again the metabolic antagonist, poses many problems which may prove to

be of extreme importance. That pantothenic acid is in some way intimately tied up with adrenal function seems certain from the data presented. How important this may be in many human maladies remains to be explored. J. F. MUELLER

The Effect of Pantothenic Acid Deficiency on Gastric Secretion and Motility. G. H. M. Thornton, W. B. Bean, and R. E. Hodges. *J. Clin. Investigation* 34: 1085, 1955.

This report is based on the experiment described in the previous abstract and is concerned with rather elaborate and special studies on the effect of induced pantothenic acid deficiency in human beings on gastric secretion and motility. Two of three subjects studied developed marked depression of gastric secretion, this decrease being contributed to by both parietal cell and non-parietal cell sources. Pepsin secretion was diminished in response to histamine and insulin but not to a test meal. Since adrenal insufficiency is associated with decreased gastric secretions, and pantothenic acid deficiency is associated with adrenal depression, this may then be the cause of these observations. However, the authors feel that another explanation might be that there is a deficiency in the parietal cell of the gastric muscosa necessary for proper secretory activity, and that this substance might be coenzyme A which could be the site of action of pantothenic acid. This, of course, is unproved at the present but is an interesting hypothesis.

There was no significant alteration in gastric motility as a result of pantothenic-acid deficiency in human beings. J. F. MUELLER

Necrosis of adrenal cortical tissue has been observed in experimental pantothenate depletion. Increased sensitivity to insulin in hypoadrenocorticism in these preparations may reflect the reduced levels of hepatic glycogen which follows removal of the glucocorticoids.

Effect of Pantothenic Acid Deficiency on Insulin Sensitivity and Response to ACTH of Intact and Diabetic Rats. R. L. Hazlewood, L. L. Bennett, and M. M. Nelson. *Endocrinology* 58: 427, 1956.

This paper is concerned with studies which were designed to elucidate the role of pantothenic acid in adrenocortical hormone secretion. The problem has been approached by studying the effect of varying degrees of pantothenic-acid deficiency on insulin sensitivity in intact and partially pancreatectomized diabetic rats. The findings demonstrate that in the early stages of pantothenic acid deficiency there is increased resistance to insulin administration but that later when the rats were severely depleted of this vitamin, insulin sensitivity was greater than in control animals. These results are interpreted as indicating hyperfunction of the adrenal cortex during the early phases of pantothenic acid deficiency but hypofunction later.

The studies reported here provide further *indirect* evidence to support the idea that pantothenic acid is concerned with adrenocortical steroid secretion. Direct measurement of corticosteroid secretion by the adrenals of pantothenic-acid-deficient animals would, perhaps, provide more conclusive evidence than can be obtained by experiments such as those described in this paper. A. B. EISENSTEIN

Pantothenic Acid and Adrenocortical Hormone Secretion. A. B. Eisenstein. *Endocrinology* 60: 298, 1957.

These studies were carried out because it was felt that direct evaluation of adrenocortical function in pantothenic-acid-deficient animals had not been done. Weanling, male Sprague-Dawley rats were fed a pantothenic-acid-deficient diet for five weeks. One group of control rats was pair-fed with the deficient group and a second control group was fed *ad libitum*. At the end of the experimental period, animals from all groups were sacrificed and the adrenals removed. The adrenals were incubated with ACTH *in vitro* and steroid hormone secretion determined. It was shown that total steroid hormone secretion by the adrenals of pantothenic-acid-deficient rats was less than that of *ad libitum*-fed or pair-fed controls. Since it is known that pantothenic-acid deficiency results in diminished tissue stores of coenzyme A, it is suggested that coenzyme A depletion is directly responsible for the decreased steroid hormone synthesis in pantothenic acid deficient animals. AUTHOR

Lipogenesis is inhibited in uncontrolled diabetes. The availability of an excess of acetate derived largely from fatty acid breakdown creates conditions favoring the formation of cholesterol from this precursor. The addition of pantothenic acid may, by increasing coenzyme A concentrations, facilitate the reaction. However, in diabetic acidosis, one would expect the production of coenzyme A to be significantly depressed.

A Possible Role of Pantothenic Acid in Diabetic Cholesterologenesis. S. Mookerjea and D. P. Sadhu. *Biochem. J.* 64: 6, 1956.

In the presence of relatively low concentrations of acetate, even a small amount of coenzyme A behaves as an inhibitor of cholesterol synthesis. When the acetate concentration is raised, the same small amount of coenzyme A increases cholesterol synthesis. In untreated diabetes (rat) where fatty acid synthesis is impaired, unoxidized acetate and overproduced acetoacetate partially take the route of cholesterol synthesis even though cholesterol synthesis is accelerated in diabetes. If an adequate concentration of coenzyme A is made available in alloxan diabetes, synthesis of cholesterol from its potential precursors may be further accelerated. To test this hypothesis, the effect of dietary pantothenic acid on the level of cholesterol in the blood and tissues of normal and diabetic rats was evaluated. The data indicate that a large excess of

calcium pantothenate (4 mg/10 g stock diet) did further increase the levels of cholesterol above the already increased levels obtained in the diabetic rats and that the levels of acetoacetate in the urine of the diabetic rats were markedly decreased by pantothenate.

M. K. HORWITT

NUTRITION IN INFANCY AND CHILDHOOD

The nutritional demands peculiar to infancy and during the years of growth and development have received much attention. Energy requirements are very high, nearly three times those of adults in terms of body weight. The amino acid intake must be properly balanced in order to assure proper conditions for protein synthesis. With a protein food such as milk supplying an adequate amino acid balance, 2 g of protein per kg/day is satisfactory; with vegetable proteins and solid foods, 3 g/kg is recommended. Some of the important factors influencing the requirements for accessory foods factors and more recent concept of dietary interrelationships in infant nutrition are described in the following paper.

Nutritional Requirements in Early Life (Borden Award Address). L. Emmett Holt, Jr., *Pediatrics* 17: 578, 1956.

Nutrition in health is a relatively minor problem compared to that in disease. In disease, organs of digestion, assimilation, and utilization are affected, and this may place limitations on particular foods or specifically influence nutritional requirements. Examples of nutritional alterations in disease include increased caloric and nitrogen demands in fever, demineralization in acidosis, potassium losses from cells in a variety of conditions, resistances to vitamin D and abnormal requirements of vitamins C and D in prematures. Choline is only needed for methylation in methionine deficiency, and folic acid is needed only when bacterial flora is diminished in the gastrointestinal tract or when vitamin C is inadequate. Vitamin B_{12} is needed only when pernicious anemia is present.

There are only a few acceptable syndromes associated with amino acid deficiencies, including fatty liver, especially with methionine deficiency; cataract and corneal vascularization have been associated with particular amino acid deficiencies, and neurologic disorders with valine deficiency. It appears certain now, after a period of uncertainty, that phenylketonuria is attributable to tyrosine deficiency resulting from a lack of the enzyme which converts phenylalanine to tyrosine; the defect in hair pigment in this condition is correctable with tyrosine supplement. There is evidence pro and con concerning the relationship of aspermatogenesis with arginine deficiency.

By producing harmless "subclinical deficiency," minimal requirements for thiamine and riboflavin and six amino acids have been evaluated. Daily excretion studies have been used successfully in studying thiamine and riboflavin requirements. It was observed that 30 per cent of thiamine is spared by substitution of fat for carbohydrate within the limits of common pediatric practice. During infection with weight loss, the excretion of riboflavin is increased as a result of tissue breakdown; therefore, this vitamin is needed only during convalescence. On the other hand, thiamine is required in active disease. Further observation with vitamin B establish that pyridoxine is a dietary essential in humans, and that nicotinic acid is not, except when tryptophan is inadequate; inadequacy of the latter was measured by decreased urinary excretion of N-methyl nicotinamide (NMN). In pellagra a diet with 15 per cent casein and no nicotinic acid is adequate for supra-minimal excretion of NMN. Lactalbumin and lactoglobulin exceed casein in their tryptophan content. Additional nicotinic acid is unnecessary and perhaps objectionable, because additional methylation is required.

Amino acid fortification of vegetable protein is perhaps advantageous or even necessary, but amino acid imbalances may result from unnecessary fortification; lysine, has been observed by Rose to increase the urinary excretion of cystine (cystinuria), arginine, and ornithine. It appears that currently publicized needs of lysine as a dietary supplement in infancy are based on studies which revealed minimal requirements which are now known to be 50 per cent less, i.e., 96 mg/kg.

J. N. ETTLEDORF

In studies such as the following, it is essential that the type of protein malnutrition and conditioning factors affecting its development are clearly understood. This disorder assumes a variety of clinical forms in different parts of the world; it is probable that antibiotic therapy, effective in one group, would show little benefit in another.

Antibiotic Dietary Supplements in the Therapy of Childhood Protein Malnutrition. R. A. Lewis, M. P. Bhagat, M. M. Wagle, B. S. Kulkarni, and R. S. Satoskar. *Am. J. Trop. Med. & Hyg.* 5: 483, 1956.

Ten children suffering from protein malnutrition (including kwashiorkor) were treated with oxytetracycline and chlortetracycline for two months. Compared to a similar group treated by conventional (dietary) means alone, the antibiotics-treated group showed a more rapid and extensive rise in hemoglobin and plasma albumin leves. The rate of clinical recovery also seemed to be more rapid.

The authors suggest that it is of significance that kwashiorkor develops when a child is weaned. The withdrawal of breast milk causes a profound change in intestinal flora. If this is one of the factors operative in the precipitation of kwashiorkor, then oral antibiotics may produce their salutory effect by again altering the flora.

S. O. WAIFE

The ability to adapt to a suboptimal intake of calories, nitrogen, and other nutritional factors is well known. Decreases in physical activity, growth rates, and cellular

metabolism make it possible for a reduced dietary intake to maintain nutritional equilibrium. It is apparent that normal levels of growth and development require higher levels of intake than those described nutritive despite the demonstration of a positive balance in these studies.

The Metabolism of Nitrogen, Calcium and Phosphorus in Undernourished Children. I. Adaptation to Low Intake of Calories, Protein, Calcium and Phosphorus. H. B. N. Murthy, S. K. Reddy, M. Swaminathan, and V. Subrahmanyan. *Brit. J. Nutrition* 9: 203, 1955.

This paper deals with studies on the metabolism of nitrogen, calcium, and phosphorus in five undernourished girls, aged seven to nine years, subsisting on a poor vegetarian diet based on rice. The mean daily calorie intake was 1,010 cal.

During the preliminary experimental period the quantities of food consumed by the subjects were weighed in order to obtain an idea of their usual food intake. During the collection period, weighed quantities of food equal to the average daily individual consumption observed in the preliminary period were given to each subject. Samples of the cooked food preparations equivalent to the mean quantities consumed by the subjects were collected daily. These were dried in an air oven at 70 to 80°, weighed, powdered, and analyzed for nitrogen, calcium, and phosphorus. Samples of rice, ragi, pulses, and vegetables used in the experiments were also analyzed separately for the above constituents. Carmine was used as a marker for the collection of feces. A check on the proper collection of urine was maintained by determining the daily excretion of creatinine in urine.

The mean daily nitrogen intake and retention were 3.0 and 0.28 g, respectively. All the subjects maintained a positive balance. The mean daily intake and retention of calcium were 200 and 23 mg, respectively. One of the five subjects maintained a negative balance. Four subjects maintained positive phosphorus balance, and one was in negative balance. The mean daily phosphorus intake was 567 mg and the average retention was 62 mg. B. SURE

The Metabolism of Nitrogen, Calcium and Phosphorus in Undernourished Children. II. The Effect of Supplementary Groundnut-milk Curds on the Metabolism of Nitrogen, Calcium and Phosphorus. G. Sur, S. K. Reddy, M. Swaminathan, and V. Subrahmanyan. *Brit. J. Nutrition* 9: 210, 1955.

The metabolism of nitrogen, calcium, and phosphorus was studied in six pairs of girls, aged 8 to 11 years, comparable in age, height, weight, and nutritional status, fed on a poor vegetarian diet based on rice or on the same diet supplemented with 12 oz groundnut-milk curd daily. The mean daily nitrogen intake on the rice diet and on the rice-groundnut curd diet was 3.60 and 5.16 g, respectively. One of the six subjects on the rice diet maintained a negative nitrogen balance, whereas all the six subjects on the rice-groundnut curd diet maintained positive balance. The daily nitrogen retention on the rice-groundnut curd diet (0.73 g) was significantly higher than that on the rice diet (0.28 g).

The mean daily intakes of calcium on the rice diet and on the rice-groundnut curd diet were 382 and 776 mg, respectively. One of the six subjects on the rice diet was in negative balance. All the subjects on the rice-groundnut diet maintained positive balance. The mean daily retentions of calcium on the rice diet and on the rice-groundnut diet were 73 and 233 mg, respectively; the difference, however, was not statistically significant.

The mean daily intake of phosphorus on the rice and on the rice-groundnut curd diet was 546 and 776 mg, respectively. One of the six subjects in the rice group maintained positive balance. The mean daily phosphorus retentions on the two diets were 57 and 116 mg, respectively, the difference being statistically significant. B. SURE

The Nutrition of Nigerian Children, with Particular Reference to Their Energy Requirements. B. M. Nicol. *Brit. J. Nutrition* 10: 181, 1956.

The present paper reports the results of an investigation designed to compare the state of health and of nutrition of peasant children from different parts of the Nigerian bush with those of the offspring of educated families living in towns.

The diets of three groups of Nigerian peasant children living in the bush country and one group of schoolchildren living in a large town were measured. The methods used to determine their average daily intake of calories and nutrients are described in the text. The general clinical condition of each group was assessed, together with the mean height, weight, pelvic intercristal diameter, skinfold thickness, hemoglobin concentration, total protein content of the plasma, and erythrocyte sedimentation rate. It is suggested that the calorie requirements of the children in their own environment are greater than those suggested by the Food and Agriculture Organization of the United Nations.

Generalized xerosis was associated with a low intake of vitamin A; angular stomatitis, nasolabial seborrhea, and an abnormal degree of injection in the conjunctiva, with a low intake of riboflavin. A relationship between gingivitis and dietary ascorbic acid deficiency was not observed, nor was any simple association demonstrated between dental caries and the consumption of cereals and calcium.

By Caucasian standards the mean hemoglobin concentration of all the groups of children was low, and the total plasma proteins and erythrocyte sedimentation rates were high. B. SURE

PYRIDOXINE DEFICIENCY

Pyridoxine is an important factor in amino acid and protein metabolism. In the coenzyme form, pyridoxal phosphate, the reactions of transamidation and decarboxyl-

ation are catalyzed. Of the numerous reaction sequences of this type which have been demonstrated in mammalian tissues, those involving tryptophan metabolism have received the most attention. In pyridoxine deficiency one of the earliest signs is the excretion of xanthurenic acid following a tryptophan load. A relationship between impaired tryptophan metabolism and neural function has been postulated. The formation of 5-hydroxy tryptamine (serotonin) requires pyridoxal phosphate as coenzyme in the decarboxylation of tryptophan. Since serotonin may play an important role in neuronal activity, certain of the cerebral and neuropathic manifestations found in pyridoxine deficiency may be explained. Isonicotinic acid hydrazide (INH) used in the treatment of tuberculosis has been found to increase the excretion rate of pyridoxine compounds in amounts up to ten times that of controls. Neuropathy may develop during INH therapy which responds to treatment with pyridoxine.

Metabolism of C^{14}-Labeled Isoniazid in Vitamin B_6-Deficient Rats. I. U. Boone, M. Magee, and D. F. Turney. *J. Biol. Chem.* 221: 781, 1956.

Previous authors have noted a syndrome resembling vitamin B_6-deficiency during treatment of tuberculosis with high doses of isoniazid which was alleviated by administration of pyridoxine. Similar observations of the antagonism of isoniazid and pyridoxine have been made in studies of bacterial enzymes and in work with animals. The present study is an attempt to evaluate the mechanisms involved in this antagonism.

Six-week-old rats were made vitamin B_6-deficient by feeding deoxypyridoxine. Isoniazid labeled with C^{14} in the carbonyl group was administered to these animals and to controls after which the distribution of the C^{14} activity in the blood and the various tissues was evaluated. Ninety per cent of the C^{14} activity was excreted in the urine six hours after injection of isoniazid. Although the results indicated a slightly decreased rate of metabolism of the drug in the vitamin B_6-deficient rats, no complete explanation for the increased toxicity of isoniazid in vitamin B_6-deficient rats could be found. M. K. Horwitt

The average daily intake of pyridoxine has been found to be 1.5 mg. It is problematical as to whether this intake is sufficient to meet metabolic needs, particularly during periods of stress.

The Relation Between Tryptophan Metabolism and Vitamin B_6 in Various Diseases as Studied by Paper Chromatography. M. Wachstein and S. Lobel. *Am. J. Clin. Path.* 26: 910, 1956.

Metabolites of tryptophan metabolism were isolated from urine by the modified Makino and by the most recent Dagliesch procedures. Only the fluorescent metabolites were studied by paper chromatography. Normal persons (controls) did not excrete fluorescent intermediary metabolites of tryptophan in their urine. The urine specimens of 6,350 unselected patients were tested; but only twenty-four yielded positive diazo reactions; only eleven of those patients were found to have 3-hydroxykynurenine in the urine, contrary to reports of Dagleish and Tekman that every positive diazo reaction is due to the presence of 3-hydroxykynurenine. Specimens of urine from 44 patients with various diseases were tested after tryptophan load tests; only 16 patients excreted urine with a positive diazo reaction due to free or acetylated 3-hydroxykynurenine. In the 28 patients with negative reactions xantheurenic acid was excreted but not 3-hydroxykynurenine. Administration of pyridoxine provoked the disappearance of 3-hydroxykynurenine from the urine of patients who had excreted it before. The authors believe that the limiting factor for stepwise catabolism of tryptophan is the amount of available vitamin B_6, even in normal subjects. Their data suggest that in hyperthyroidism, febrile diseases, or in neoplasia less vitamin B_6 is available due to an increased rate of catabolism. The present experiments did not include pregnant subjects; the role of the fetal-maternal competition in the availability of vitamin B_6 still requires elucidation.

It appears that there might be an open field for the study of the human genetics of such tryptophan metabolism, especially the cases of spontaneous excretion of 3-hydroxykynurenine. Fundamental biologic research with lower forms of animals and some plants have revealed critical relationships between genes and the enzymes involved in tryptophan metabolism.

E. Cohen

The clinical importance of pyridoxine was highlighted a few years ago by the discovery that convulsions and neurologic disorders appearing in infants receiving a certain type of feeding would be reversed by the administration of the vitamins. The pyridoxine content of milk used in preparation of the feed was destroyed in the processing of the product. There are many problems involved in determining requirements of this vitamin in human nutrition in view of the difficulties involved in assay.

Vitamin B_6 in Sterilized Milk and Other Milk Products. A. Z. Hodson. *J. Agriculture and Food Chem.* 4: 876, 1956.

In 1952, 1953, and 1954 a manufacturer of a sterilized and canned infant formula encountered a problem in infant nutrition which appeared to be due to partial destruction of vitamin B_6 (or pyridoxine) during processing of the product, since the convulsions noted in infants consuming such processed milk were relieved by vitamin B_6 therapy. Such clinical experience has resulted in modification of commercial processing operations of canned sterilized milk which would insure the least destruction of this essential vitamin for infant welfare.

The pyridoxine (vitamin B_6) content of fresh and processed milk was studied by the author ten years ago. At that time the chemistry and physiology of pyridoxine seemed to be reasonably well worked out, but a short

time later other members of the vitamin B_6 group (pyridoxamine, pyridoxal, and pyridoxic acid) were discovered and synthesized. Since then knowledge of the chemistry and physiology of vitamin B_6 has increased. In addition to the three forms of the vitamin, there are a number of phosphorylated and conjugated forms that are difficult to estimate quantitatively.

Two microbiologic assay methods for vitamin B_6 have been slightly modified to conform to the newer knowledge of the vitamin and the metabolic requirements of the assay organisms. The modified methods give similar but not necessarily identical results when applied to fresh or pasteurized milk or non-fat dry milk solids, but different results when applied to stored evaporated milk. Experimental work suggests that pyridoxal of fresh milk is changed progressively to pyridoxamine and then to an unknown form of vitamin B_6, during processing and storage of evaporated milk. The unknown form of the vitamin is not equally active for the assay organisms. B. SURE

NUTRITION AND DENTAL HEALTH

One of the important public health advances has been that of the fluoridation of water supplies in many of the metropolitan areas in this country. Almost without exception, there has been a striking reduction in caries-susceptibility in the children of these communities. Studies have shown that the fluoride content of water is reflected in the fluoride content of teeth and the caries resistance appears to be related to the latter factor.

The Evanston Dental Caries Study. XVI. Reduction in Dental Caries Attack Rates in Children Six to Eight Years Old. I. N. Hill, J. R. Blayney, and W. Wolf. *J. Am. Dent. A.* 53:327, 1956.

Since the water supply in Evanston was fluoridated in February 1947, it was not possible prior to 1955 to study the dental experience rates of children exposed to fluoridated water during the prenatal and postnatal periods. Altogether 1,376 children were examined in the six- to eight-year-old group and found to have a decayed, missing and filled (DMF) tooth index of 53.86 per 100 children. Comparable age groups of children in Evanston in 1946 had a DMF rate of 149.76. The results were even more striking among the six-year-old children where the DMF rate in 1955 was 6.58 per 100 children in comparison to 46.85 per 100 children in 1946. Among both the six- and seven-year-old children the DMF rate in the 1955 evaluation at Evanston was appreciably lower than the DMF rate for six- and seven-year-old children in Aurora in 1945 and 1946 where the water naturally contained 1.2 parts per million of fluoride. The eight-year-old children in Evanston in 1955 had a caries index almost identical with the eight-year-old children in Aurora a decade earlier. This is another striking example of the influence of fluoridation of a public water supply on the dental caries experience of children growing up in that area The close similarity to results obtained earlier in an area where the water naturally contained fluorides is another strong endorsement for the value of thorough epidemiologic studies followed by thorough field trials of the effectiveness of the agent investigated.

J. H. SHAW

A Controlled Study into the Effect of Dental Health Education on 1539 School Children in St. Albans. H. C. Davis, G. J. Parfitt, and P. M. C. James. *Brit. Dent. J.* 100:354, 1956.

An intensive effort was made in this community of St. Albans, where there was a low fluoride water supply, to determine to what extent dental health education was effective in the child population. The results were evaluated by means of a questionnaire to determine to what degree the dental health habits of the children had been changed by the educational experience. Throughout the survey the oral health standards were consistently higher among the girls. As a result of the educational program the standards have improved considerably among both boys and girls, though the results were more striking for the girls. The program was most effective in inducing the children to brush their teeth more frequently but much less effective in inducing them to reduce their intake of candy and cakes between meals. J. H. SHAW

The type and composition of the diet occupies a most important place in the dental caries index of children. Careful dietary control with foods high in protein and fat and low in carbohydrate result in a lower caries' index than in groups not placed under such dietary supervision. It is probable that the lowering of carbohydrate intake is less important than the provision of an adequately balanced nutritional intake.

The Food Habits and Dental Status of Some Connecticut Children. M. Potgieter, E. H. Morse, F. M. Erlenbach, and R. Dall. *J. Dent. Res.* 35:638, 1956.

The dental status and food habits of 864 children in eastern Connecticut were surveyed. The dental examinations were made by public health dental hygienists with the use of good light, mouth mirrors and explorers but no x-ray. The dietary data were collected from seven-day booklets that were filled in by the children. The scoring of the diets was based on the basic seven food groups. The optimal diet for a child was postulated to contain 13 servings distributed through the basic seven food groups in a desirable ratio. The children were grouped into three areas in proportion to the number of servings of the basic seven foods consumed per day. Those in the "high" group consumed between 9 and 13 servings, those in the "middle" group between 7.0 and 8.9 and those in the "low" group from 3.0 to 6.9. When the city and country children were grouped together 358 fell in the high group, 317 in the middle and 189 in the low group.

The rural children on the average had appreciably better diet rating scores. A positive relationship between the present dental status and the general quality of the diet was observed. For example in the "high"-diet group, 208 of the children had from 0 to 6 decayed, missing and filled (DMF) teeth, while in the "low"-diet group only 62 fell in this dental rating. Among the children who had 13 to 24 DMF teeth, 8 per cent were in the high-diet group and 27 per cent in the low-diet group. There was also a relationship between milk consumption and dental status with the children consuming higher levels of milk per day having better teeth in general. There was also a modest relationship between the dental status and the total fruit and vegetable consumption. J. H. SHAW

There is no agreement on the role of the lactobacillus organisms in the production of dental caries. Extensive investigations upon this aspect of cariogenesis continues with some evidence that lactobacilli immunity may reduce caries formation. The finding of increased amylolytic activity in the saliva of caries-susceptible experimental animals introduces another important variable.

The Isolation and Classification of Lactobacillus Strains from Italian Saliva Samples. A. C. Hayward and G. H. G. Davis. *Brit. Dent. J.* 101:43, 1956.

Saliva samples were collected from 66 individuals in Rome, Italy. Nineteen of the individuals in this group were considered to be completely free from caries. Fourteen of the saliva samples contained no lactobacilli as determined under the conditions of the experiment. Seven of these samples were collected from individuals with caries-free mouths and seven from individuals with lesions. Altogether 386 strains of lactobacilli were isolated and classified from these salivary samples. Of these only 11 strains could not be identified in terms of already published data. This is an interesting observation in view of the fact that there are appreciably different dietary habits represented among these Italian individuals than would be true from similar surveys conducted in England or in America. J. H. SHAW

Salivary Lactobacillus Counts and Snyder's Caries Susceptibility Test, and Their Relationship to Dental Caries Incidence during a Period of 12 Months. G. L. Slack and W. J. Martin. *Brit. Dent. J.* 101: 111, 1956.

The controversy over whether or not there is a direct relationship between lactobacillus counts in the saliva and the dental caries susceptibility of patients continues. In the present paper studies are reported where bacteriologic examinations of the saliva of approximately 100 children in a residential home in Liverpool were conducted over a period of a year and a half to two years. In the main part of the study 84 children were observed for one year. No definite association between the lactobacillus count of the saliva or of Snyder's test and the development of caries in the following 6 to 12 months was observed. These authors conclude that neither of these tests can be used under the circumstances tested by them to forecast the likely incidence of dental caries in individual cases.

J. H. SHAW

A Study of the Bacterial Flora of Caries-Susceptible and Caries-Immune Saliva. G. E. Green and M. C. Dodd. *J. Dent. Res.* 35:572, 1956.

A comparative study was made of the microflora in the saliva of 25 caries-immune and 25 caries-susceptible human adults. Gram-negative diplococci occurred with greater frequency in the immune saliva. Caseolytics occurred with comparable frequency in immune and susceptible salivas. Gram-negative rods, yeasts, streptococci, micrococci, aerobic and anaerobic lactobacilli all occurred with greater average frequency in the saliva from caries-susceptible mouths than in the saliva from caries-immune mouths. In the case of yeasts and the anaerobic lactobacilli, this difference was on the borderline of statistical significance. However, the difference in the case of the aerobic lactobacilli was statistically significant. The rough types of lactobacillus colonies were almost never seen on plates from immune saliva but 55 per cent of colonies from susceptible saliva were of the rough type. In other studies a mixture of immune saliva and varied media was inoculated with a lactobacillus culture and incubated. A distinct increase in light transmission was noted which was taken to indicate that there had been an inhibition of lactobacillus growth by the immune saliva. No comparable effect was observed when susceptible saliva was incubated under comparable circumstances. The authors postulated that the inhibitory effects of immune salivas could account for their lower numbers of lactobacilli and thus indirectly produce the low caries rates of caries-immune individuals.

This is an extremely detailed investigation and is to be commended because of the detail with which other oral microflora than the lactobacilli are studied.

J. H. SHAW

Morphologic and Enzymatic Differences in Caries-Resistant and Caries-Susceptible Albino Rats. L. M. Sreebny, J. Meyer, and E. Bachem. *J. Am. Dent. A.* 53: 9, 1956.

Inbred strains of rats with predictable caries-susceptibility have become vital in caries research. However, there is little information to point out why these strains differ so strikingly from one another in their susceptibility to dental caries under experimental conditions. In the present study it was found that the submaxillary glands in animals from a caries-susceptible strain have the same degree of amylolytic activity but five times as high proteolytic activity as the submaxillary glands from the caries-resistant strain. In addition, the submaxillary glands from caries-susceptible animals had a higher proportion of intralobular duct tissue. It was postulated that these findings might be at least a partial explanation for the difference in caries-

susceptibility between the offspring of these two strains of rats. This is an area that needs intensive investigation during the next few years, until the full relationship of the constitutional differences between strains and the caries-susceptibility of the strains has been fully evaluated. J. H. SHAW

Decreased Activity of Dental Caries in Desalivated Albino Rats. J. C. Muhler and D. Bixler. *J. Dent. Res.* 35:615, 1956.

The influence of the removal of the salivary glands and of the removal of the maxillary molars was compared in albino rats fed a coarse particle corn diet. It was shown two decades ago that in intact animals the removal of the maxillary molars of rats fed a coarse diet resulted in an almost complete prevention of tooth decay. Where the maxillary molars were present, a normal incidence of carious lesions occurred in the mandibular molars. These data indicated that the opposing teeth were necessary in order to force the coarse particles into the fissures of the teeth sufficiently firmly to establish a locus for the formation of carious lesions. In the present study this experimental condition was repeated with rats from which the salivary glands had been removed. Sialoadenectomy from a variety of other studies is known to be a severe penalty to the teeth. Yet where the maxillary molars were absent in this experiment as well as in the older one, a striking reduction in caries was observed. This finding indicates the need for a specific mechanical influence for the production of carious lesions with a coarse particle diet, even in the absence of a normal salivary flow.

In another experiment pair-fed intact and sialoadenectomized rats were fed a high sucrose purified diet. No teeth were removed in either group. Under the pair-feeding circumstances, the removal of the salivary glands did not cause as destructive a carious process as has been reported in other experiments.

J. H. SHAW

The Distribution of Lead in Human Enamel. F. Brudevold and L. T. Steadman. *J. Dent. Res.* 35: 430, 1956.

The lead content was measured in different layers of enamel prepared from groups of unerupted and erupted teeth by a spectrographic procedure. In all groups of teeth the outer layers of the enamel contained higher amounts of lead than the inner layers. For example, in the outer layer of enamel from teeth extracted from individuals in the 20 to 29-year age group, there were 360 parts per million (p.p.m.) of lead, in contrast to 34 p.p.m. in the ninth layer from the surface. This differential existed in unerupted teeth as well as in erupted ones. The amounts of lead in unerupted teeth were appreciably lower than in erupted teeth; likewise, the levels in incompletely formed unerupted teeth were lower than in fully formed unerupted teeth. Among erupted teeth, there was an appreciably higher amount of lead in the various enamel layers of teeth from older people than in comparable layers of teeth from younger age groups. The level for the outer enamel of the group of teeth from subjects over 50 was 550 p.p.m., in contrast to 350 p.p.m. for the same layer from people under 20 years of age. This observation indicates a post-developmental increase of lead in the enamel that is not explainable on the basis of calcification or cellular remodelling, unlike the situation in bone. The amount of lead was found to be somewhat lower in a group of erupted fluorosed teeth than the values observed for normal teeth. The latter finding may indicate a geographic distribution in the amount of lead available for distribution through the calcified tissues. On the other hand, it may indicate that fluorides interfere with the process whereby lead accumulates in the enamel. Naturally, the overall question is concerned with whether or not there is any nutritional significance to the presence of lead in enamel. J. H. SHAW

Effect of Tryptophan Deficiency on Bones and Teeth of Rats. II. Effect of Prolongation. L. A. Bavetta and S. Bernick. *Oral Surg., Oral Med., Oral Path.* 9: 308, 1956.

Seven-week-old rats were maintained for periods varying from 3 to 26 weeks on a tryptophan-deficient diet. The controls were fed the same diet supplemented with DL-tryptophan. The experimental animals lost approximately 50 per cent of their original weight, and 50 per cent of these developed cataracts. A narrowing and premature closure of the epiphyseal plate was noted after five weeks on the deficient diet. Progressive osteoporosis was observed in the long bones with intense manifestations by the sixteenth to twenty-sixth weeks. A gradual replacement of the myeloid elements of the marrow spaces by fatty tissue had occurred. Osteoporosis of the spongiosa of the alveolar bone was found routinely. By the eighth week only a shell of the alveolar bone remained. By the sixteenth week, the alveolar bone had been fragmentized into small islands of bone which appeared as isolated osteogenic centers with a loss of attachment for many of the periodontal attachment fibers of the inter-radicular bone.

It would be interesting to know if the above findings in tryptophan deficiency were specific or whether similar or identical ones might not occur in a comparable degree in deficiency of any essential amino acid or of protein. It also is of more than passing interest to know what happened to the rate of eruption and to enamel and dentin formation and calcification in the incisors of these deficient animals. J. H. SHAW

PHENYLKETONURIA

(The reader is referred to the important observations of Armstrong, Low, and Bosma elsewhere in this issue.—Ed.)

This disease is one of the gene-linked inborn errors of metabolism. In this condition there is an inherited deficiency of a hepatic enzyme required for the conversion of

phenylalanine to tyrosine. The interruption of this amino-acid interconversion results in an abnormal accumulation of certain aromatic degradation products of phenylalanine in the serum. The toxicity of these compounds is reflected in their effects upon the central nervous system. The following papers provide further evidence that dietary restriction of phenylalanine containing foods may be capable of reversing the abnormalities produced in this disease. The early recognition of the congenital disorder may permit the institution of the diet prior to the development of neurologic manifestations.

Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria. Clinical Observations in Three Cases. F. A. Horner and C. W. Streamer. *J. A. M. A.* 161: 1628, 1956.

Phenylketonuria is a condition in which mental deficiency is associated with an inherited abnormality in the metabolism of the amino acid phenylalanine. This paper reports observations on three patients with phenylketonuria who were treated with a phenylalanine-restricted diet. The levels of the amino acid in the serum were lowered to and maintained near the normal range. At the time of this report, two preschool children who had been treated for nine and ten months were showing improvement in objective behavior. In addition, both became psychologically testable. The electroencephalogram was normal in one child; in the other, in which it was abnormal, it returned to normal after the dietary program was instituted.

A sibling of one of these children was followed from birth. When the urinary ferric chloride test became positive at the age of eight weeks, the child was placed on a phenylalanine-free diet. This infant shows normal motor and mental development thus far.

This paper, together with a few others also reporting improvement on a phenylalanine-restricted diet in this condition, would seem to indicate that an important step has been taken in the nutritional management of this rare but important disease. S. O. WAIFE

Phenylalanine-Restricted Diets in the Treatment of Phenylketonuria. J. D. Blainey and R. Gulliford. *A. M. A. Arch. Dis. Child.* 31: 452, 1956.

Clinical and biochemical histories in great detail are presented for six children with congenital phenylketonuria. They were treated for a period up to four years with phenylalanine restriction. Extensive metabolic studies of weight, nitrogen balance, plasma phenylalanine and the excretion of phenylalanine, indole and phenolic compounds are presented for two of the children.

The abnormal plasma and urinary findings typical of the disease can be completely corrected by limiting the intake of phenylalanine to levels of 15 mg/kg/day and the diet on which this was achieved is detailed. On this intake normal weight gain and nitrogen metabolism can be maintained. High-carbohydrate diets are essential, 70 per cent of calories being given as carbohydrate in a diet providing 110 cal/kg daily. Treatment at home for long periods has proved difficult.

In two cases mental testing gave clear evidence of an accelerated development and in three cases more limited changes such as better motor control and a decrease in mannerisms occurred. Regression occurs when dietary control is relaxed. Treatment is most successful when commenced at an early age. F. E. HYTTEN

Although phenylketonuria is commonly manifested at a very early age, the following observations suggest that the congenital abnormality may occur in a milder form which may escape recognition. A correlation between the severity of the process and hepatic tissue levels of hydroxylase would be of interest in these cases.

Phenylketonuria. Two Unusual Cases. N. L. Low, M. D. Armstrong, and J. W. Carlisle. *Lancet* 2: 917, 1956.

Two cases of phenylketonuria are described: a girl two and one-half years of age and a man 50 years of age. The girl was discovered accidentally during medical examination for suspected tuberculosis and the man during the screening of inmates of an institution for the condition. The girl appeared to have a normal intelligence, the man had an I. Q. of 67.

Biochemical findings suggest that these cases are able to metabolize at least some of the injected phenylalanine, so that the condition is probably not an all-or-none phenomenon. This may explain the greater mental ability of these two cases compared to others previously described in the literature.

F. E. HYTTEN

The failure of tyrosine administration to improve the neurologic status of phenylketonuric patients provides further support for the hypothesis that the metabolic products of phenylalanine metabolism are responsible for these symptoms.

The Effect of Tyrosine Administration in Phenylketonuria. S. E. Snyderman, P. Norton, and L. Emmett Holt, Jr. *A.M.A. Am. J. Dis. Child.* 90: 616, 1955 (Soc. Trans.).

The nature of the metabolic defect in phenylketonuria is now reasonably well established. The hepatic enzyme hydroxylase is missing, as a result of which phenylalanine is not converted to tyrosine. The phenylalanine of the blood rises to extremely high levels, and this amino acid together with a number of aromatic degradation products is excreted in quantity in the urine.

The relation between the symptomatology of the disease and the metabolic error is still a matter of dispute. It is possible that the relation is a coincidental one; the symptoms have also been attributed (1) to an excess of phenylalanine, (2) to toxic metabolic products, and (3) to a deficit of tyrosine. Suggestive evidence of neurologic improvement on a restricted phenylalanine

diet has been published, but the observations on this point are still equivocal.

Four phenylketonuric subjects between two and six years of age were given dietary supplements of L-tyrosine by mouth in quantities of 1 g per kg/day. All of these patients exhibited the characteristic blond hair, although they came from families with dark complexion. This dietary supplement resulted in the appearance of dark hair at the root margins. After three months the supplement was discontinued, following which the new hair growing out was pigmented. No evidence of neurologic improvement was associated with the tyrosine supplementation. Paper chromatographic studies of the urine showed no change except for an increased excretion of tyrosine.

It is concluded that at least a part of the symptomatology of the disease can be attributed to tyrosine deficit. The observations are, however, compatible with the view that other related aromatic compounds compete successfully with tyrosine in enzyme systems.

J. N. ETTELDORF

POTASSIUM METABOLISM

An intimate relationship has been found to exist between chronic potassium-deficiency states and pyelonephritis. In patients with primary aldosteronism, prolonged diarrhea and Fanconi syndrome, renal biopsy specimens have disclosed evidence of chronic pyelonephritis. Experimental potassium depletion in rats has been demonstrated as a factor predisposing to renal infection, the biochemical lesion produced by hypokalemia and low tissue potassium levels lowers renal resistance to infection by an unknown mechanism.

Chronic Renal Disease in Rats Following a Temporary Deficiency in Potassium. P. Fourman, R. A. McCance, and R. A. Parker. *Brit. J. Exper. Path.* 37: 40, 1956.

Growing rats were fed a potassium-deficient diet to which exchange resin was added in order to remove potassium that might be present in the body. After two months, the animals were put back on a stock diet. Renal changes, apparently of a chronic pyelonephritic type, developed; the lesions were limited in extent after several weeks of observation, but became more severe as time went on. Although such lesions are common in untreated old rats, the kidneys of the control animals were unaltered.

M. SILBERBERG

Most cases of potassium-losing nephritis are really examples of primary aldosteronism manifested by muscular weakness, hypertension, alkalosis, hypokalemia, and evidence of renal functional disorders. It is of considerable significance that potassium depletion itself is responsible for renal disturbances. On the other hand, intrinsic renal diseases such as tubular acidosis, malignant nephrosclerosis, Fanconi syndrome, and the diuretic phase of tubular necrosis are capable of producing excessive potassium losses, with the attendant biochemical disturbances reflected in many phases of metabolism.

Potassium-losing Renal Disease. R. F. Mahler and S. W. Stanbury. *Quart. J. Med.* 25: 21, 1956.

The case is described of a 63-year-old woman who, from a combination of anorexia and renal loss of potassium, became depleted of about one-half her total body potassium. Her symptoms included muscular paralysis, dehydration, and nocturia. She was submitted to an extraordinarily detailed metabolic study.

The principal biochemical abnormalities in the plasma were a low potassium level (as low as 1.8 meq/liter) and a hypophosphatemia; the blood-urea level was normal and, despite an inability to produce maximally acid urine, there was no metabolic acidosis. The biochemical abnormalities were corrected, and all the symptoms but nocturia were relieved, by giving potassium bicarbonate and a low-sodium diet.

Detailed metabolic and renal studies, before and during potassium replenishment, allowed the separation of renal abnormalities attributable to the renal disease (shown by biopsy to be chronic pyelonephritis) from secondary functional disturbances resulting from the potassium deficiency.

Potassium deficiency appeared to be responsible for reversible renal phosphaturia, impaired capacity for sodium conservation, and possibly reduced osmolar concentrating capacity. The renal mechanisms responsible for potassium loss are discussed in detail.

The effects of potassium deficiency on nitrogen and phosphorus metabolism were studied, and observations were made on the carbohydrate metabolism of the weakened muscles. Those observations appeared to establish the indispensibility of potassium for the synthesis of protein in man, and suggested a relationship between body potassium and the capacity for phosphate absorption by the renal tubules and possibly the bowel. No abnormality of excitability or disturbance of lactic acid formation could be demonstrated in the weak, potassium-depleted voluntary muscles. This unique study is presented in very great detail and is essential reading for workers in electrolyte metabolism.

F. E. HYTTEN

Extensive losses of tissue potassium occur in diabetic acidosis while serum levels remain normal or become elevated. Other medical disorders with low-tissue potassium not reflected in serum levels may escape recognition as indicated in the following report.

Serum-Potassium Levels as an Index of Body Content. C. T. G. Flear, W. T. Cooke, and A. Quinton, *Lancet*, 1: 458, 1957.

Although experiments demonstrate that acute depletion of potassium is reflected in the serum level, in clinical practice where depletion is often gradual this may not be so. In three groups of patients with congestive heart failure, steatorrhea and a miscellaneous

collection of medical disorders, the serum potassium level measured by flame photometry was compared with the total body potassium measured by an isotope dilution method. There was no correlation.

"Clinical awareness of the circumstances likely to lead to potassium depletion is the most important factor in its diagnosis. Clinical symptoms and signs and serum biochemical findings are of secondary importance."

F. E. HYTTEN

One of the best sources of potassium for oral therapy is meat broth or bouillon; among fruits, prunes and prune juices provide a high concentration of this electrolyte.

Oral Potassium Therapy. C. T. G. Flear, M. Hill, and G. Thomas. *Lancet* 2: 1190, 1956.

There are many clinical conditions in which potassium depletion occurs and where replacement is required. There are considerable difficulties associated with giving large quantities of it by mouth, the usual ones suggesting gastrointestinal irritation.

Various potassium salts are suggested but none has been found acceptable by all patients. In general, the more seriously ill the person, the lower the tolerance. In an effort to find some natural source of potassium which would be helpful in therapy a large number of proprietary drinks, including alcoholic ones, were analyzed for Na, K, and Cl and this very useful list is published. In general the pure fruit juices contain the most potassium with the least sodium.

F. E. HYTTEN

Dietary Sodium and Potassium in California Wines. P. S. Lucia and M. L. Hunt. *Am. J. Dig. Dis.* 2: 26, 1957.

The sodium and potassium content of 277 samples of various types of wines were analyzed by flame photometry. Two hundred and fifty-nine California wines, nine musts, and nine samples of foreign table wines made up the series. The sodium content of 164 table wines ranged between 0.97 and 24.15 mg/100 ml (average 5.5 mg/100 ml or 2.39 meq/liter), while the potassium content ranged between 28.15 and 157.96 mg/100 ml (average 93.72 mg/100 ml or 24.1 meq/liter). Dessert wines were slightly higher in sodium and slightly lower in potassium concentration. The authors point out the advantage of using wines to add flavor to the low-sodium diet.

J. B. HAMMOND

Tissue utilization of potassium is increased by testosterone in conjunction with the anabolic activity promoted by the hormone. Since this is a gradual process, a decline of serum potassium levels would not be expected such as has been noted with glucose and insulin which produce a rapid change in cellular metabolism and potassium uptake.

The Concentration in Plasma of Potassium and Calcium During Testosterone Medication. H. G. Keitel. *J. Lab. & Clin. Med.* 49: 96, 1957.

This is a short concise paper with negative results. A previous report in the literature had stated that three of twelve children given methyl testosterone or testosterone propionate had a reduction in serum potassium to below 1 mM per liter. The authors present data on 10 prepubertal children given either methyl testosterone or testosterone propionate over a minimum of 30 days. There was a significant increase in body weight denoting an anabolic effect but no change in the concentration of serum potassium. Serum calcium was also measured and proved to be normal. No explanation can be offered for discrepancy of results between this study and previously reported results obtained by others.

K. R. CRISPELL

The following appears to be a very precise demonstration of the effect of digitalis upon potassium transfer as hypothecated by Szent-Györgyi. The effectiveness of the digitalis glycosides in the failing myocardium may be related to their capacity for regulating the rate of potassium movement into the cell.

Effects of Digitalis and Hypoxia on Potassium Transfer and Distribution in the Dog Heart. H. L. Conn, Jr. *Am. J. Physiol.* 184: 548, 1956.

The effects of moderately severe hypoxia and moderately large doses of digitalis on potassium kinetics and distribution in the left ventricle of the normal intact dog were studied after the apparent establishment of a new steady state. Digitalis and hypoxia, more so, caused reduction in interstitial-intracellular potassium transfer rates and rate constants, and modest to moderate reduction in cell and interstitial potassium. Hypoxia also caused marked increase in plasma-interstitial potassium exchange rate and rate constants apparently due to the increased coronary blood flow resulting from hypoxia. The effects of digitalis on ISF-ICF transfer are compatible with the thesis that a major action of digitalis is the partial inhibition of potassium transfer into the myocardial cell. The results from the steady state hypoxia experiments show that aerobic metabolism is necessary for at least a considerable fraction of potassium transfer in the heart.

AUTHOR